EVALUATION OF 3 COMMONLY USED MOUTHWASHES USED IN TREATING CHEMO RADIOTHERAPY INDUCED MUCOSITIS – A RANDOMIZED CONTROL STUDY

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CERTIFICATE

This is to certify that this dissertation entitled "**Evaluation of 3 commonly used mouthwashes used in treating chemo radiotherapy induced mucositis – A randomized control study**" is a bonafide record of work done by **Dr. P. Jagathesh**, post graduate student in the department of oral medicine and radiology, Ragas Dental College & Hospital, under my supervision during his post graduate study period between 2007-2010.

This dissertation is submitted to **THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,** in partial fulfillment for the degree of **Master of Dental Surgery in Branch VII - Oral Medicine and Radiology**.

It has not been submitted (partial of full) for the award of any other degree or diploma.

Guided by:

Dr. Capt. S. Elangovan, M.D.S
Professor,
Dept of Oral Medicine & Radiology,
Ragas Dental College & Hospital,
Chennai – 600119.

Capt. S. ELANGOVAN, M.D.S.
PROFESSOR
DEPT. OF ORAL MEDICINE & RADIOLOGY
RAGAS DENTAL COLLEGE & HOSPITAL
CHENNAI-600 119.

Dr. S. Shanmugam, M.D.S
Professor & Head,
Dept of Oral Medicine & Radiology,
Ragas Dental College & Hospital,
Chennai – 600119.

Dr. S. SHANMUGAM, MDS.,
Prof. & H.O.D Oral Medicine & Radiology
RAGAS DENTAL COLLEGE & HOSPITAL
2/102, East Coast Road, Uthandi
Chennai-600 119

Dr. S. Ramachandran, M.D.S
Principal,
Ragas Dental College & Hospital,
Chennai – 600119.

PRINCIPAL
RAGAS DENTAL COLLEGE & HOSPITAL
CHENNAI

Place: Chennai
Date: 20.11.2009

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ABBREVIATIONS

S.No	Abbreviations	Expansions
1.	ANOVA	Analysis of variance
2.	cGy	Centi Gray
3.	CHX	Chlorhexidine Group
4.	Gys	Gray
5.	HIV	Human Immuno Virus
6.	MeV	Mege electron Volt
7.	mL	Milli litre
8.	“m” M	Magic mouthwash
9.	QS	Quantity sufficient
10.	SD	Standard Deviation
11.	Soda	Salt/Sodium bicarbonate group
12.	TNM	Tumor Node Metastasis
13.	WHO	World Health Organization
14.	X^2	Chi square test

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Cancer is a known condition characterized by uncontrolled cell growth and spread of abnormal cells. Head and neck is a predilected site for a large number of cancers among which the squamous cell carcinomas predominate in the oral cavity. Patients with cancer in the head and neck can be treated with surgery, chemotherapy, radiotherapy, or a combination of both treatment modalities[32].

Oral mucositis is a common side effect of cancer therapies, particularly radiation therapy for head and neck and various forms of chemotherapy. It commonly results in severe pain that can compromise the duration and success of cancer management[31].

Oral mucositis is defined as oral mucosal change secondary to cancer therapy. It manifests first by thinning of oral tissues leading to erythema. As these tissues continue to thin, ulceration eventually occurs. Inhibition of cell growth and maturation by radiation and chemotherapy disrupts the primary mucosal barrier of the mouth and throat, creating a pathway for the establishment of oro-pharyngeal infection by resident oral microflora. Consequences of this include oral mucositis and gingivitis, oral candiasis, xerostomia, trismus, dental caries, osteoradionecrosis, cellulitis, and viral mucosal eruptions. These oral complications may cause significant patient discomfort, poor nutrition, delay in administration or dosage limitations in antineoplastic treatments, increased hospitalization stays and costs, and in some patients, life-threatening septicemia[14].

In addition, severe mucositis may require temporary or permanent cessation of radiation or chemotherapy before completion of the planned treatment regime. This is of a marked concern, as there is strong clinical and radio-biologic evidence that protraction of overall treatment time has adverse influences on the curability of certain human tumors, particularly squamous cell carcinoma of the head and neck region[4].

For prophylaxis of oral mucositis, various agents are used in order to reduce the incidence and severity of mucositis[25]. Sodium bicarbonate reduces the acidity of the oral fluids immediately. It dilutes accumulating mucus and discourages yeast colonization. Chlorhexidine gluconate is an antimicrobial agent that appears to be effective in controlling early periodontal infections. Hydrogen peroxide, once recommended as an oral rinse to aid in the management of adhesive mucus and the oxygenation of the oral tissues, has recently come into dispute because of its possible carcinogenic and its ant fibroblast healing – delaying action[5].

Anecdotal reports suggested that the 'magic' mouthwash which consisted of "mixtures" aimed at producing analgesia or anesthesia and coating the inflamed and painful oral mucosa. There is not much evidence existing to support the efficacy of this mixture in the treatment of mucositis. The 3 most common ingredients in these mixtures are viscous lidocaine solution, diphenhydramine hydrochloride and aluminum hydroxide suspension. However, because the use of these agents is common in clinical practice, this combination could be a material of choice for treating mucositis[9].

An ideal oral rinse for patients with head and neck malignancies should reduce the oral micro flora, promote re-epithelization of soft tissue lesions, normalize the pH of oral fluids, have an acceptable taste, and be nontoxic[5]. A preliminary study reported that alcohol-free mouthrinses cause less patient pain than those containing alcohol. It is accepted that tobacco and alcohol are two risk factors for oropharyngeal cancer; however, the association between cancer and the use of alcohol – containing mouthrinses is still being evaluated[4].

Alcohol is used in mouthrinses as a dissolvent of other ingredients and as an antiseptic agent. Its presence on mouthrinses is detrimental to patients with mucositis, who are immunocompromised, or are sensitive to the ingredient. Its use is also contraindicated in patients undergoing radiations therapy for head and neck cancers, which is known to cause xerostomia, ulcerating gingivitis, and tissue damage. These conditions may be exacerbated by alcohol. Ethanol can also contribute to surface softening and can increase wear of dental caries and composite materials[4].

The development and use of alcohol free mouthrinses are relatively new. Certain studies have shown their efficacy and lack of side effects, but there is no clear confirmation[6]. The present study was done to find the effect of three alcohol free mouthwashes on radiation and combination therapy induced oral mucositis in patients with head and neck malignancies.

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Treatment of head and neck cancer represents a significant challenge to the oncologist because of the poor prognosis, associated medical problems and adverse effects of treatment on patient function and appearance[17]. Patients often are treated in a multidisciplinary clinic. Treatment usually consists of a combination of surgery, chemotherapy and radiation therapy. The aim of the treatment is to cure the patient while maintaining as much function of the involved organs as possible. If surgery and radiation therapy offer similar cure rates, the cosmetic and functional sequelae of the different treatment modalities influence the approach chosen. If the cancer is advanced and cure is not possible, the treatment goal is palliation[17].

Radiotherapy is done by using ionizing radiation in the treatment of cancer[6]. The ionizing radiation produce their tumoricidal effects by virtue of their direct ionizing effect on the DNA of the cell as well as their indirect effect on the cell membrane, which is mediated by free radicals generated by the hydrolysis of water in the tissues[6]. Although both tumor tissue and normal tissue suffer from radiation induced damage, the lack of repair capacity in the undifferentiated tumor tissue renders the radiation damage permanent. The presence of repair mechanisms in the normal tissue enables them to get away with minimal radiation induced damage provided the radiation is given in small doses separated by a definite time interval[6]. When the dose of radiation exceeds the specific radiation tolerance dose of normal tissues it leads to side effects which are invariably permanent. The effect and benefits of radiation are not immeidate[17]. Typically, more aggressive tumors, whose cells divide rapidly, respond more quickly to radiation. Radiation therapy is painless and does not make the patient radioactive.

Radiotherapy consists of two broad treatment modalities namely Teletherapy and Brachytherapy[3]. In Teletherapy the patient is placed at a distance of 80-100 cm from the radiation generating equipment which contains either a radioactive source (co-60 gamma radiation produced by a Telecobalt machine) or generates high energy X rays and electrons (as in the Linear accelerator) [3]. The advantage of Teletherapy is that the divergence of the radiation beam resulting from the large treatment distance enables treatment of a large tumor bearing area (eg Buccal mucosa and neck) to a uniform dose. The disadvantage of Teletherapy is that some amount of normal tissue irradiation and hence normal tissue side effects are unavoidable. The essence of treatment planning lies in minimizing the dose to normal tissue while ensuring that the tumor tissue is delivered the tumoricidal dose[3]. Modern forms of Teletherapy such as 3D Conformal Radiotherapy and Intensity Modulated Radiotherapy as well as advances in imaging such as MRI and PET scan have played an important role in radiation dose escalation to tumor tissue without exceeding normal tissue tolerance.

In Brachytherapy the radioactive source is placed in contact with the tumor bearing tissue. The small size of the radioactive source used, coupled with the principle of inverse square law, which states that the radiation intensity is inversely proportional to the square of the distance from the radiation source: results in the radiation being concentrated on the tumor with rapid dose fall off and sparing of normal tissue. The advantage of Brachytherapy is that it delivers high conformal dose of radiation to the tumor with maximal normal tissue sparing. The disadvantage of Brachytherapy lies in that it can be used as a primary radiation modality only in early cancers as it is effective only in small tumor sizes.

In advanced malignancies the tumor is first shrunk with Teletherapy and wherever feasible Brachytherapy is added in the second phase of radiation as a boost to the tumor bed to improve the local control[21].

Radiation therapy is important in the cure of the patient with head and neck cancer for several reasons. First, most head and neck cancers are radiosensitive. Carcinomas limited to the mucosa, exophytic and well – oxygenated tumors have a high cure rate with radiation[17]. Radiotherapy alone is used as a curative modality in stage I and II of head and neck cancers as the cure rates are equivalent in comparison with surgery and in addition the anatomy and physiology are preserved[6]. In stage III and IV cancers Radiotherapy is used as an adjuvant (Post – Op / Pre – OP) to surgery as bone and muscle involvement alters the responsiveness of the tumor and decreases radio curability. However if surgery is not feasible then alternatively patients suffering from locally advanced head and neck cancers with good general condition are subjected to chemo – radiation treatment. Patients suffering from systemic head and neck cancers are palliated mainly with radiotherapy[6].

As every treatment has its side effects, so does radiotherapy. The most important acute effect is mucositis which is particularly problematic and is a real issue for patients, potentially compromising nutrition and having a negative impact on cure rates as well as quality of life[17]. Added to these are the potential problems associated with the late radiotherapy related side effects, such as xerostomia, tooth decay, soft tissue fibrosis and, rarely, osteonecrosis of mandible. However in spite of the side effects, Radiotherapy shall remain an inseparable

component of head and neck cancer therapy particularly in developing countries where the majority of patients present with advanced cancer.

Radiotherapy – induced mucositis decreases the quality of life by impairing eating, swallowing, and talking and by disturbing sleep. Mucositis may also predispose to local and systemic infections and may cause interruption of radiotherapy course. Years of research work have concentrated to find the pathogenesis, associated morbidity factors and prevention of oral mucositis induced by radiation therapy in patients with head and neck malignancies. An attempt has been made to cite a few of them below.

Pathogenesis of mucositis

Dobbs et al[8] in 1989 suggested that the majority of new cases of invasive head and neck cancer will need radiotherapy as a primary treatment, as an adjunct to surgery, in combination with chemotherapy, or as palliation The radiation dose needed for the treatment of cancer is based on location and type of malignancy, and whether or not radiotherapy will be used solely or in combination with other modalities. Most patients with head and neck carcinomas, treated with a curative intent, receive a dose between 50 and 70 Gray (Gy). This dose is usually given over a five to seven – week period, once a day, five days a week, 2 Gy per fraction. The most important dose limiting factor is the tolerance of the adjacent normal tissues. Depending on stage and location of the primary tumor and affected lymph nodes; the oral cavity, salivary glands, and jaws of most head and neck cancer patients may be located in the radiation portals. Even with the most

optimal radio therapeutic schedule, unwanted radiation induced changes will occur in these tissues.

Dorr and Kummermehr in 1990[3] using a mouse model explained the mucosal changes following radiation as follows. The lack of formation of new basal cells caused by radiotherapy leads to a gradual, linear decrease in cell numbers. If the cellularity of the mucosa drops below 70% of the normal level, the cell production rate from the surviving cells increases dramatically (a possible cause for the whitish aspect of oral mucosa). As radiotherapy continues, a steady state between mucosal cell killing and mucosal cell regeneration may occur and favour an acute reaction in the form of a prominent erythema. Around the third week of radiotherapy, more severe symptoms of mucositis, such as the formation of pseudo membranes and ulceration, may appear. Various signs of mucositis may emerge during radiotherapy. The first clinical signs of mucositis occur at the end of the first week of a conventional seven – week radiation protocol (daily dose of 2 Gy, Five times a week). There is no consensus regarding what is the first clinical sign of mucositis. Some authors describe a white discoloration of the oral mucosa, which is an expression of hyperkeratinization as the first symptom, followed by or in combination with erythema. Others consider erythema to be the first reaction.

Dorr and Kummermehr (1990)[3] in their study also explained the development of pseudo membranes, when radiotherapy commences, as a cell regeneration process that cannot keep up with cell killing. As a result, partial or complete epithelial denudation develops, which presents as spotted or confluent pseudo membranous mucositis.

Maciejewski et al in 1991[20] and Riesenbeck et al in 1998[27] suggested pseudo membranes to be ulcers covered by fibrinous exudates. Others suggest that pseudo membranous mucositis is related to yeast stomatitis or to colonization of the oral cavity with Gram negative bacilli.

Sonis 1998[35] considered mucositis to be a 4 step process consisting of the following phases-

Phase I: Initial inflammatory / vascular phase: During this phase, exposed cells (epithelial, endothelial, and connective tissue cells) in the buccal mucosa release free radicals, modified proteins, and pro inflammatory cytokines, including interleukin – 1B, prostaglandins, and tumor necrosis factor (TNF). These inflammatory mediators cause further damage either directly or indirectly by increasing vascular permeability, thereby enhancing cytotoxic drug uptake into the oral mucosa.

Phase II: Epithelial phase: In this phase, chemotherapy and / or radiation retards cell division in the oral mucosal epithelium, leading to reduced epithelial turnover and renewal, resulting in epithelial breakdown. This results in erythema from increased vascularity and epithelial atrophy 4 to 5 days after the initiation of chemotherapy. At this stage, micro trauma from day to day activities such as speech, swallowing and mastication leads to ulceration.

Phase III: Ulcerative / bacteriological phase (Pseudomembraneous): Epithelial breakdown ultimately results in the ulcerative phase, which occurs within 1 week of therapy. Loss of epithelia and furious exudation lead to the formation of pseudo membranes and ulcers. In this phase, microbial colonization of damaged mucosal surfaces by Gram – negative organisms and yeast occurs,

and this may be exacerbated by concomitant neutropenia. There are numerous reports that demonstrate the importance of ulcerative mucositis as an etiologic factor in the development of systemic α - hemolytic streptococcal infections in cancer patients.

Phase IV: Healing Phase: The duration of this phase usually lasts from 12 to 16 days, and mainly depends on factors such as epithelial proliferation rate, hematopoietic recovery, reestablishment of the local microbial flora, and absence of factors interfering with wound healing viz infection and mechanical irritation. Healing eventually occurs from the surviving mucosal steam cells. Similar changes have been observed in humans, in whom the mucositis is characterized by loss of epithelial cells, absence of vascular damage, and an inflammatory reaction at the epithelial – connective tissue interface.

Denham et al[7], in 1999 suggested that the severity of mucositis varies considerably between patients and may relate to the fractionation schedule applied. Accelerated fractionation results in a more rapid onset of mucositis. Furthermore, the mucosa of the oral cavity does not react in the same manner at all locations. Mucositis is most severe in the soft palate, followed, in order, by the mucosa of the hypo pharynx, floor of the mouth, cheek, base of the tongue, lips, and dorsum of the tongue. Patients with compromised oral mucous membranes secondary to alcoholism and / or excessive smoking exhibit the most severe mucosal changes.

Handschel et al[18], 1999 suggested that radiation induced oral mucositis is characterized by atrophy of squamous epithelial tissue and an inflammatory infiltrate concentrated at the basement region. Damage to oral mucosa is strongly related to radiation does, fraction size, volume of irradiated tissue, fractionation scheme, and type of ionizing irradiation[44]. Oral side – effects develop early during radiotherapy. The acute mucosal response to radiotherapy is a result of mitotic death of epithelial cells, since the cell cycle time of the basal keratinocytes is about four days.

Steel et al[39] in 2002 suggested that tissues with rapid turnover rates show acute reactions to radiotherapy (early effects), while in tissues with slower turnover rates, damage may not become evident for months or years after therapy (late effects). One of the most important acute effects of radiotherapy on the oral mucosa is radiation induced mucositis. Mucositis induced by radiotherapy is defined as the reactive inflammation of the oral and oropharyngeal mucous membrane during radiotherapy in the head and neck region. Radiotherapy induced mucositis is not simply an epithelial process; rather it involves micro vascular injury resulting from endothelial – cell apoptosis, increased peripheral blood levels of tumor necrosis factor a and interleukin – 6 and genetically induced differences in the rates of tissue apoptosis.

Role of Infection:

Spijkervet et al[33] in 1989 suggested that mucositis is basically a tissue reaction to the trauma of radiation or chemotherapy. Other factors that may contribute to the development of mucositis include the increase in the inflammatory mediator, platelet activating factor in saliva of irradiated patients; leukocyte adhesion to E selection or endothelial intercellular adhesion molecule – 1 (ICAM -1) which promotes the radiation induced inflammatory response in squamous epithelium; a decrease in the level of salivary epidermal growth factor; and an increase in the carriage rate of Gram negative bacilli in the oropharynx (among other Enterbacteriaceae, Pseudomonaceae).

Spijervet et al[34] in 1991 suggested that marked increase in oral Gram negative enterobacteria and pseudomonas could be shown as a possible aggravating factor for development of oral mucositis. Less than 10% of healthy individuals exhibit colonization of the oral cavity with these non indigenous Gram negative bacilli. This is due to the oropharyngeal colonization defense, which is determined by the integrity of the anatomical structures, physiology, motility, secretions secretary immunoglobulin A, mucosal cell turnover, and the indigenous flora. These factors are impaired by radiotherapy for head and neck cancer and are negatively influenced by more generalized factors, such as advanced age, medical interventions (e.g., surgery) and underlying disease. Selective elimination of Gram negative bacilli was associated with a reduction of pseudo membranes and ulceration. These authors postulated that Gram negative bacilli or endotoxin released by Gram negative bacilli could pay a major role in the development of

the advanced stages of radiation mucositis, while the initial signs are basically related to irradiation only.

Ramirez – Amador et al [26] in 1997 suggested that the most common infection in the oral cavity during or shortly after radiotherapy is candidiasis. They showed that the prevalence of positive candida cultures increased from 43% at baseline to 62% at completion of radiotherapy and to 75% during the follow up period. Some authors believe that oral mucositis is aggravated by fungal infections. However, treatment of yeast and Gram positive cocci with topical anti fungals and disinfectants failed to relieve such complications. Thus, many of the oral lesions observed during treatment do not seem to be due to candidiasis or streptococcal infection. Finally it should be mentioned that herpes simplex virus infection is not a significant contributing factor in irradiation mucositis. This is in contrast to the commonly seen herpes simplex virus reactivation following chemotherapy and chemo radiotherapy patients.

Evaluation of Mucositis:

In routine clinical practice as well in the area of research, proper assessment of oral mucosa is of paramount importance before initiating radiation therapy to the head and neck regions, as well as chemotherapy. Comparisons of the toxicity of treatment regimens as well as evaluation of various modes of intervention for mucositis have been hindered by the lack of a universally acceptable scoring system for the condition.

More than 15 different mucositis scales are currently used. Some are based solely on objective (Ulceration and erythema), or descriptive findings (pseudomembrane formation), whereas others depend on symptomatic interpretation or analgesic or functional outcomes, and others still are driven by nursing management endpoints. Presently, the grading system most commonly used to describe oral mucosal toxicity associated with radiation and chemotherapy treatment regimens is the WHO Scale, which combines symptoms, function, and objective findings to arrive at a score[13].

The presumed complexity of mucositis scoring is reflected by the fact that different National Cancer Institute (NCI) Common Toxicity Criteria exist for oral mucositis associated with head and neck radiation, chemotherapy, and bone marrow transplant conditioning regimens. Establishment of a common, accepted scale is critical as a benchmark for both describing regimen toxicities and for studies in which mucositis treatment are evaluated.

A variety of protocols and grading systems have been introduced, but only a few of them are standardized and validated. A good scoring system is that which will consider all patient related factors viz. the patient's physical and nutritional status combined with a detailed inspection of the oral cavity. Clinical severity of mucosal injury will vary from mild, moderate and severe conditions.

Various grading systems for scoring the severity of mucositis are as follows

1. World health organization (WHO) grading of mucositis
2. National cancer institute toxicity criteria for grading stomatitis
3. Radiation therapy oncology group (RTOG) oral mucositis grading system
4. Oral assessment guide (OAG)
5. Objective scoring system for the site assessment

World health organization (WHO) grading of mucositis is the universally accepted method for assessing the severity of mucositis.

World Health Organization (WHO) grading of mucositis[13]

This scoring system is widely used in routine clinical practice and clinical trials for the evaluation of mucositis. It is grated from 0 to 4 as follows-

Grade 0	No symptom.
Grade 1	Soreness and erythema.
Grade 2	Erythema, ulcers; can eat solid foods.
Grade 3	Ulcers, requires liquid diet only.
Grade 4	No possible alimentation.

Chemoradiotherapy - dosages and regimens

Tanguay Y Seiwert et al (2007) [36] explored the use of chemoradiotherapy in head and neck cancer stating that the advent of chemoradiation has significantly contributed to the curability of head and neck cancer, including locoregionally advanced disease. The article also reviews the available chemoradiotherapy standards used for head and neck cancer, which initially focus on single-agent cytotoxic-based regimen and later on multiagent-based regimens. The present focus is on preserving organ function and reducing toxic effects. The guidance for clinicians based on current clinical trial evidence on how to choose appropriate treatment platforms is also provided.

Ryan and Burri (2009) [28] in their review article on chemotherapy and radiotherapy for patients with head and neck cancer stated that more than 500,000 cases were reported to have diagnosed with cancer. Head and neck cancer require a multidisciplinary setting to manage. Various combinations for managing such patients include surgery, radiotherapy, chemotherapy and more recently the biologic therapy. The ultimate aim of treatment included minimizing tumor control while maintaining function and quality of life. Most patients with locally advanced disease, and multimodality organ conserving therapy were often employed for these patients. This article focuses on the rationale and evidence supporting the use of concurrent chemotherapy in the management of locally advanced head and neck cancers.

Radiation induced mucositis and its management

Wolfgang J. Kostler et al (2001) [44] in their over view on options for prevention and treatment of oral mucositis stated that oral mucositis represents a major non-hematologic complication of cytotoxic chemotherapy and radiotherapy associated with significant morbidity that may delay the treatment plan itself. The article narrates the incidence, pathogenesis and predisposing factors for oral mucositis. The prophylactic and therapeutic armamentarium for the treatment of oral mucositis which consists of locally and systemically applied nonpharmacological measures and pharmacotheraputics are also discussed.

Trotti et al (2003) [38] in his systematic review to determine the frequency of mucositis and associated outcomes in patients receiving radiotherapy for head and neck cancer collected the randomized clinical trials of patients with head and neck cancer receiving radiation therapy with or without chemotherapy that were reported. 33 studies were included which met with the inclusion criteria. Mucositis was defined using a variety of scoring systems. It was found that the mean incidence was 80% and only 56% patients experienced severe mucositis among the patients who were treated with altered fractionation compared with 34% of conventional radiotherapy. Rates of hospitalization due to mucositis were reported only in 3 studies and it was 32% for patients treated with altered fractionation and 16% for conventional radiotherapy. 11% of patients had altered fractionation regimens interrupted or modified because of mucositis in 5 studies. It was concluded that mucositis is a frequent toxicity in patients with head and neck cancer and it may lead to hospitalization and treatment interruptions.

Spencer W. Reeding (2005) [31] in his review article on cancer therapy related oral mucositis stated that oral mucositis is a common side effect of cancer therapies, particularly radiation therapy for head and neck cancer and various forms of chemotherapy. It manifests first by thinning of oral tissues leading to erythema. As these tissues continue to thin, ulceration eventually occurs. It commonly results in severe oral pain that can compromise the duration and success of cancer management. The author also reviewed the current concepts on the epidemiology, pathophysiology, prevention and treatment of cancer related oral mucositis.

Comparing various scoring systems for mucositis

Spijkervet et al (1989) [32] defined irradiation mucositis as an inflammatory-like process of the oropharyngeal mucosa following therapeutic irradiation of patients who have head and neck cancer. Clinically, it is a serious side effect because severe mucositis can cause generalized problems (weight loss, nasogastric tube feedings) and interferes with the well-being of the patient seriously. Grading mucositis is important for the evaluation of preventive and therapeutic measures. The object of this study was to develop a scoring method based on local mucositis signs only. Four clinical local signs of mucositis were used in this score: white discoloration, erythema, pseudomembranes and ulceration. Mucositis of the oral cavity was calculated during conventional irradiation protocol for 8 distinguishable areas using the 4 signs and their extent. A prospective evaluation of this method in 15 irradiated head and neck cancer patients displayed an S-curve reflecting a symptomless first irradiation week,

followed by a rapid and steady increase of white discoloration, erythema and pseudomembranes during the second and third week. Oral candidiasis, generalized symptoms such as weight loss and the highest mucositis scores were seen after 3 weeks irradiation. The novel mucositis scoring method may be of value in studying the effect of hygiene programs, topical application of disinfectants or antibiotics on oral mucositis.

Durmus Etiz et al (2002) [13] stated that aggressive cancer treatment may have toxic effects on normal cells as well as cancer cells. Radiation induced mucositis is the most important acute side effect in patients undergoing radiotherapy for head and neck malignancies. There are number of scoring systems, although none is universally accepted and all lack standardization. A prospective study was conducted to evaluate the validity and reproducibility of 5 different mucositis scoring systems. The samples were 43 patients with head and neck malignancies who had been irradiated were evaluated. 5 different mucositis scoring systems which included WHO, Radiation Therapy Oncology Group, “Hickey”, “Van deer Schueren” and “Makkonen” were compared with each other. It was concluded that all scoring systems were equally valid and the exact grading of mucositis can be achieved by combining clinical information about pain and nutritional status with oral mucosal reactions.

Relation Between alcohol and alcohol containing mouthwashes and oral and pharyngeal cancer

Weaver et al (1979) [40] in his study among 200 patients with squamous cell cancer of the head and neck, 11 persons abstained from all alcoholic beverages and tobacco. All but one of these 11 patients had used mouthwash many times daily for more than 20 years. Most of them used a brand of mouthwash that contained 25% alcohol. This evidence, along with information from other patients, may be used to confirm or refute the theory that mouthwash may be carcinogenic for susceptible persons.

Bolt et al (1983) [2] conducted a case-control study in North Carolina a part of it, involving 206 women with oral and pharyngeal cancers and 352 controls, questions were asked concerning the patterns of mouthwash use. No significant overall increase in risk was found among users; the relative risk, adjusted for snuff dipping and smoking habits, was 1.15 [lower, upper limits of the 95% confidence interval (95% Cl) = 0.8, 1.7]. The relative risk associated with mouthwash use was increased to 1.94 (95% Cl = 0.8, 4.7), however, among women abstaining from tobacco. Although consistent dose-response relationships were not observed for this subgroup, these findings and other reports of an increased risk among persons ordinarily at low risk of this disease raise the possibility that mouthwash may contribute to oral and pharyngeal cancers.

Wynder et al (1983) [43] conducted a retrospective study to evaluate the role of mouthwash and other factors in relation to oral cavity cancer. Daily use of mouthwash showed an excess risk in females but no excess risk in males. No dose response was seen in females with increased duration of use. In nonsmoking,

nondrinking women as well, daily mouthwash use was associated with excess risk. Multiple logistic regressions including all factors of interest showed inconsistent results for duration and frequency of mouthwash use. Due to the absence of a dose-response relationship and the possibility of confounding by tobacco and alcohol use, it was not possible to attribute causal significance to the association between daily mouthwash use and oral cancer in women.

Mashberg A et al (1985) [23] studied the relationship between alcohol and oral and pharyngeal cancer. 96 patients with oral and pharyngeal cancer and 986 control patients were interviewed regarding mouthwash use, commercial brand of mouthwash frequently used, alcohol and tobacco consumption, and demographic characteristics. Analysis of results showed use of mouthwash was not significantly different between those with oral and pharyngeal cancer and control group. Similar results were also observed in patients with similar smoking habits, and those who consumed alcohol. Thus this study demonstrates little association between use of mouthwash and oral and pharyngeal cancers.

Deborah M. Winn et al (1991) [42] in their survey on mouthwash (alcohol containing) use and oral conditions in the risk of oral and pharyngeal cancer interviewed 866 patients with cancer of the oral cavity and pharynx and 1249 controls of similar age and sex from the general population in 4 areas of the united states since tobacco smoking and alcohol consumption were the primary causes for oral and pharyngeal cancer in the United States. Risk of oral cancer was elevated by 40% among male and 60% among female mouthwash users, after adjusting for tobacco and alcohol consumption. It was found that risks among

both sexes increased equally in duration and frequency of mouthwash use and were confined to users of mouthwash high in alcohol content. It was concluded there is an association between mouthwash containing alcohol and oral cancer.

Winn DM et al (1991) [42] evaluated oral health practices and use of alcohol – containing mouthwashes as risk for developing oral and pharyngeal cancers. Data was collected by a structured questionnaire from 1114 oral cancer cases and 1268 controls regarding tobacco use, alcohol use, diet, occupation and oral health status. Analysis of results showed 49% of males and 58% of females among the cases used mouthwash, the corresponding sex – specific OR { odds Ration } being 1.4 and 1.6, thus revealing a statistically significant increase in risk associated with regular mouthwash use. The risk tended to increase with increasing duration and frequency of mouthwash use and according to the alcohol concentration of mouth wash.

Use of mouthwashes in patients undergoing radiotherapy for head and neck malignancies

Samaranayake LP et al (1988) [29] in his single- blind study compared the efficacy of benzydamine and chlorhexidine in alleviating irradiation-induced mucositis in two groups of patients undergoing post-operative radiotherapy for squamous carcinoma of oral activity. In addition, quantitative and qualitative assessment of some oral flora was also done. 25 patients were randomly allocated to use either benzydamine or chlorhexidine mouthwashes twice daily for 6 weeks. Mucositis and pain was measured subjectively along with microbial samples taken by oral rinse technique every week. Analysis of results showed no significant difference in the overall mucosal rating. However 12 out of 13 patients using benzydamine recorded oral discomfort while washing the mouth as compared with 7 out of 12 in chlorhexidine group. There was no significant difference between the carriage rate of yeasts, coliforms and staphylococcus aureus when using the different mouthwashes. This study concludes that though there is little difference between the mouthwashes, chlorhexidine is preferable to patients.

Spijkervet FKL et al (1989) [32] did a prospective, double – blind, randomized, placebo-controlled study to find out the effect of chlorhexidine 0.1% rinses on viridians streptococci and yeasts, as well as enterobacteriaceae, pseudomonadaceae, and Acinetobacter spp, and staphylococci in 30 patients with cancer of the head and neck with identical radiation portals to the oropharyngeal areas. After a dental treatment deemed necessary to eliminate foci of infection or mechanical irritation, half of the patients rinsed and sprayed a chlorhexidine 0.1%

solution, while the other half with a placebo. The patients rinsed their mouth, for 1 minute, three times a day. Mucositis was evaluated and thrice weekly afterwards. Oropharyngeal cultures were also obtained at similar intervals by oral washing with isotonic saline solution and incubated at 37^{o} C for 18 hours.

Analysis of results showed that except for viridans streptococci, no significant difference was observed in the number of carriers and oral concentration among the two study populations. There was also no difference in the development and severity of oral mucositis between the two groups, thus demonstrating that 0.1% chlorhexidine rinse neither reduces the oropharyngeal flora nor the development and severity of oral mucositis.

Epstein JB et al (1989) [12], in his study**,** evaluated the effect of chlorhexidine rinse in 50 patients undergoing radiation therapy to the head and neck region and developed xerostomia. At the initial visit a complete dental evaluation and salivary flow rate data were collected. The Decay Missing Filled Surface [DMFS] was determined and saliva was submitted for determination of salivary count of S. mutans and lactobacillus species. High caries risk patients rinsed twice daily with 0.2% chlorhexidine gluconate in addition to application of neutral 0.5% sodium fluoride gel once daily. Patients were seen up to 26 times over a period of up to 3 years and salivary flow rate tests and bacteriologic study were repeated. Results showed a moderate reduction of S. mutans but limited response of lactobacillus to chlorhexidine rinse in conjunction with fluoride application.

Ferretti GA et al (1990) [15] did a double – blind randomized study to find efficacy of chlorhexidine mouth rinse in oral mucositis reduction in patients with cancer receiving either radiotherapy to the head and neck or intensive systemic chemotherapy. 70 patients, who completed the study were randomly assigned to use a mouth rinse containing either 0.12% chlorhexidine digluconate or a control rinse identical in composition but without chlorhexidine. Patients were instructed to swish vigorously and gargle 15ml of mouth rinse for 30 seconds, thrice a day for 21 days. They were followed up 1 week after the uses of mouth washes were stopped. Mucositis was scored and oral microbial assessment was done at baseline, 7, 14, and 21 days and one week after discontinuation of mouth rinses. Analysis of results showed that treatment- associated oral soft tissue inflammation and ulceration can be significantly reduced in patients undergoing chemotherapy by using chlorhexidine. However little or no reduction of mucositis was observed in patients receiving high-dose head and neck radiation therapy.

Carl W and Emrich LS (1991) [5] determined whether a specific oral care with Kamillosan Liquidum oral rinse would reduce and/or prevent the severity of radiation-induced mucositis in 20 patients scheduled to receive radiotherapy. Kamillosan Liquidum solution is prepared from the flower of the chamomile plane. The main constituents are chamazulene, levomenol, polyins, and flavonoids. The patients, after an oral examination, were instructed to use 10 to 15 drops of Kamillosan rinse in approximately 100ml of warm water at least 3 times a day along with cleaning the teeth and soft tissue with toothettes. The oral tissue changes were recorded daily for inpatients and during every clinic visit to out patients. Tissue changes were assessed on a scale of 0 to 3: measurements of pH

of oral fluids were made, as well as intraoral photographs were taken. Analysis of results showed that though one patient assigned Kamillosan Liquid mouthwash developed grade 3 mucositis, most patients who used conventional oral care with 5% sodium bicarbonate, saline and 3% hydrogen peroxide developed grade 3 mucositis, thus showing that Kamillosan oral rinse will prevent or reduce tissue inflammation and desquamation.

Toljanic JA et al (1992) [37]**,** in his study, evaluated and quantified the level of substantivity of chlorhexidine in individuals who had received cancericidal doses of radiation for tumors of head and neck. Six patients, previously treated with primary or adjunctive radiotherapy were instructed to vigorously rinse with ½ oz. of .12% chlorhexidine rinse for 30 seconds, after which they were instructed to expectorate. This was followed exactly 1 minute later by a second aqueous rinse of 1% acetic acid, which was again expectorated. The procedure was then repeated twice during which the time interval between the 0.12% chlorhexidine rinse and 1% acetic acid rinse was changed to 1 and 4 hours respectively. The expectorated acetic acid was neutralized and incubated for 18 to 24 hours in media plates containing trypticase soy agar seeded with test organism [S. epidermidis].

Measurable zones of inhibition were noted with all cycles for five of the six subjects, showing that when 0.12% chlorhexidine is used as an oral rinse in patients irradiated for certain tumors of head and neck, an antibacterial element is retained and gradually released into the oral cavity over time.

52 patients participated in the multi-institutional placebo-controlled, randomized clinical trial by **Foote RL et al (1994)** [16] to determine whether a chlorhexidine mouthwash could alleviate radiation-induced oral mucositis. Patients were randomized equally among the following three treatment groups:

i. Chlorhexidine mouthwash, 15ml four times a day throughout the period of radiation therapy and 2 weeks thereafter,

ii. Placebo mouthwash, used in the same schedule,

iii. Oral non-absorbable antibiotic lozenge containing amphotericin B, tobramycin and polymyxin E

Oral mucositis was graded according to World Health Organization criteria at baseline and at weekly intervals. In addition, patients were requested to fill out questionnaires on a weekly basis and 4 weeks thereafter. Analysis of results showed slightly more stomatitis and side effects in the chlorhexidine patients, thus ruling out the possibility that chlorhexidine can lower the average daily mucositis score.

Feber T (1996) [14]**,** in his study, randomized patients undergoing radical radiotherapy treatment (55-60Gy in 4 weeks) to more than 50% of the oral cavity and oropharynx based on a oral care protocol with either saline 0.9% or hydrogen peroxide 3.5 volumes (HP) as rinses. The results of his study showed that, on average, the group receiving saline rinses appeared to do better on some outcomes than the group receiving HP. This suggested that frequent mechanical cleansing of the mouth may be more important than the antiseptic properties of a mouthwash.

Rahn R et al (1997) [25]**,** in his monocentric, open, placebo- controlled and randomized clinical trial, enrolled 40 patients and randomly assigned them to a treatment or control group [20 patients each]. During radiation therapy, all patients received mucositis prophylaxis with nystatin, dexpanthenol, rutoside and immunoglobulin. In addition, patients of the treatment group performed 4 times daily rinsing (3min, each) with 100ml povidone-iodine solution from the beginning to 1 week after the end of radiation therapy. Patients of the control group rinsed with sterile water in the same way. Clinical examination of oral mucosa was performed before starting radiation therapy and weekly during radiation therapy until 2 weeks after the end of therapy. A last examination took place 6 weeks after the end of therapy. Mucositis was graded according to WHO recommendations. Analysis of results showed oral mucositis in 14 patients of the treatment group and in all 20 patients of the control group. The mean onset of mucositis was after 2.25 weeks in treatment group and 1.5 weeks in control group. The severity of mucositis was also statistically significant between the two groups. Thus the present study demonstrates that rinsing with povidone-iodine- in addition to a standard prophylaxis regimen reduces the incidence, severity and duration of radiation induced oral mucositis.

Adamietz IA et al (1998) [1] investigated the efficacy of prophylactic oral rinsing with povidine-iodine solution in a prospective randomized study of 40 patients scheduled to undergo radiochemotherapy of head and neck region. During radiation therapy, all patients received mucositis prophylaxix with nystatin, dexpanthenol, rutosides and immunoglobins. In addition, 20 patients in treatment group performed rinsing 4 times daily (3 min. each) with 100 ml povidone- iodine

solution while 20 patients in control group rinsed with sterile water in the same way. The severity of mucositis was defined according to the WHO recommendations and clinical examination was done before commencing radiation therapy, every week during radiation therapy and 2 and 6 weeks after the end of radiation treatment. Analysis of results showed a statistically significant higher grade of mucositis in control group. The onset of mucositis was also significantly later in povidone-iodine group with a faster recovery, thus demonstrating that povidone-iodine group, in addition to a standard prophylaxis regimen- reduces incidence, severity and duration of radiation-induced oral mucositis.

Marylin J Dodd et al (2000) [9] conducted a randomized clinical trial for evaluating the effectiveness of 3 commonly used mouthwashes to treat chemotherapy-induced mucositis. The study consisted of 200 patients from 23 patient and office settings who were undergoing stomatotoxic chemotherapy and were monitored from the time they developed mucositis until cessation of the signs and symptoms of mucositis or until they finished their 12 day supply of mouthwash. All patients were randomly assigned a mouthwash (salt and soda, chlorhexidine and "magic" mouthwash (lidocaine, Benadryl and Maalox). The nurses used the oral assessment guide for initial assessment and patients were taught how to assess their own mouth and the nurses phoned the patients every day to gather status reports among the 200 patients, there was cessation of signs and symptoms of mucositis within 12 days and there was no significant difference between the 3 compared groups and the authors concluded that with the given

comparable effectiveness of the mouthwashes, the least costly was salt and soda mouthwash.

Borrajo GLL et al (2002) [4] evaluated the efficacy of an alcohol- free chlorhexidine mouth rinse to the same preparation with 11% ethanol and a placebo. 97 patients were included in the study and were divided into 3 groups. They were asked to rinse one of the following mouth rinse: 0.12% chlorhexidine gluconate, 0.05% soldium fluoride and 11% ethanol: the same chlorhexidine formulation without ethanol: and a placebo,for 30 seconds with 10ml of undiluted mouth rinse once a day for 27 days. Baseline plaque and papillary bleeding index were recorded and repeated at 14 and 28 days. Analysis of results showed significant reduction in baseline plaque and papillary bleeding in both chlorhexidine groups when compared placebo, though there was no difference between them, showing that chlorhexidine mouth rinses with or without alcohol reduces plaque levels.

In this study, **Dodd NJ et al (2003)** [10] hypothesized that if the particles in the original sucralfate suspension were micronized (i.e., < or =25microns) then the coating action of the mouthwash in the oral cavity would be enhanced. The purpose of this pilot study was to compare the efficacy of micronized sucralfate (Carafate R) mouthwash and salt and soda mouthwash in terms of the severity of the mucositis, the severity of mucositis-related pain, and the time required to heal radiotherapy-induced mucositis in patients with head and neck cancer. Severe mucositis and related pain can interfere with the ingestion of food and fluids, so patients body weight were measured as well. All patients in this randomized

clinical trial carried out a systematic oral hygiene protocol called the PRO-SELF: mouth aware (PSMA) program. Patients who developed radiation-included mucositis anytime during their course of radiotherapy (RT) were randomized to one of the two mouthwashes and followed to the completion of RT and at one month following RT. Two referral sites were used for the study. Repeated measures occurred with the following instruments/variables: MacDibbs mouth assessment and weight. Demographic, disease and cancer treatment information was also obtained. Thirty patients successfully completed the study. No significant differences were found in the number of days to onset of mucositis (i.e., 16+/-8.4 days). When patients had their worst MacDibbs score, (i.e., most severe mucositis), there were no significant differences between the mouthwashes as to MacDibbs score, the RT dose received, are rating of pain (upon swallowing). Similarly, at the end of RT, no significant differences were found between mouthwashes as to MacDibbs score are ratings of pain (upon swallowing). At the one –month follow up assessment, no significant differences were found between the mouthwashes in MacDibbs scores are pain ratings (upon swallowing). The analysis of the efficacy of the two mouth washes revealed no significant differences in the time to heals (in days) from the RT- induces mucositis. The findings from this trail provide important clinical information regarding cost analysis of RT mucositis management. Given that there is no significant difference in efficacy between micronized sucralfate and salt and soda, use of the less costly salt and soda is prudent and cost effective.

PD. Kumar Madhan, PS. Sequeira, Kamalaksha Shenoy, Jayaram Shetty (2008) [19] conducted a randomized control trial on comparing the effect of three alcohol free mouthwashes on radiation-induced oral mucositis in patients with head and neck malignancies. The study group consisted of 80 patients with head and neck malignancies scheduled to undergo curative radiotherapy. They were randomly assigned to receive one of the 3 mouthwashes (0.12% chlorhexidine, 1% povidone-iodine or salt/soda) or a placebo which was taken as a control. The patients were instructed to rinse with 10ml of the mouthwash, twice daily, for a period of 6 weeks. Mucositis was assessed at baseline and at weekly intervals during radiation therapy based on WHO criteria for grading of mucositis. The baseline values of the 4 groups were matched for age, sex, stage of cancer. A post hoc test for repeated measures was used to find the difference of mean mucositis scores between the groups at various week intervals. It was found that povidone-iodine mouth wash had better results compared to the other groups and the placebo and it was concluded that it can reduce the severity and delay the onset of oral mucositis due to therapeutic radiotherapy.

This study was conducted between April 2008 to March 2009 in the department of Oral Medicine and Radiology of Ragas Dental College and Hospital, Dr. Rai memorial medical and Cancer Centre and Cancer Shelter, Chennai.

Study Design:

The present study is a placebo controlled and randomized controlled trial.

Study population:

60 patients with head and neck malignancies, scheduled to undergo chemo radiotherapy at Dr. Rai memorial medical and cancer centre and cancer shelter, Chennai were enrolled in the present study and randomly assigned to the test or control groups (15 patients each).

The inclusion and exclusion criteria are as follows.

Inclusion criteria:

1. Patients should be above 18 years of age.
2. Patients should have head and neck malignancies of stage III and stage IV, according to TNM classification.
3. Patients should be scheduled to receive chemo radiotherapy at Dr. Rai memorial medical and cancer centre and cancer shelter, Chennai.
4. The planned radiation dose should be equal to or exceed 60Gy, delivered at 30 fractions, spread over a 6 week period.

5. The patients who take cisplatin and 5-fluorouracil along with radiotherapy for 21 days with 2 cycle each.
6. Atleast one third of the oral cavity mucosa should be included in the radiotherapy field.
7. Patient should be able to read, and/or understand and sign the informed consent.

Exclusion criteria:

1. Patients with open mouth sores at study entry.
2. Patients who had undergone prior radiotherapy or chemotherapy.
3. Patients with HIV infections, diabetes mellitus, or hyperthyroidism.
4. Patients who are allergic to any used mouthwashes.
5. Patients using other prophylactic mouthwashes.
6. Patients who are pregnant.
7. Patients who required use of any form of treatment/medicaments (eg., antibiotics, analgesics, etc.) during the course of radiotherapy because of exacerbation of symptoms.

External beam radiotherapy:

The purpose of radiotherapy is to deliver a uniform dose of radiation to the tumor mass, while the dose received outside of the tumor zone is minimized.

At Dr. Rai memorial medical and cancer centre and cancer shelter, Chennai, external beam radiotherapy is used to treat patients with head and neck malignancies. Cobalt 60 is used as the radioactive source that emits gamma rays at an average energy level of 1.2 MeV. In addition, moulds are made for all head and

neck malignancy patients undergoing radiotherapy for immobilization of their head during radiation.

These patients received external bilateral irradiation, 2 Gys daily, for a total dose of 60 Gys: the doses given five days a week over a period of 6 weeks. The irradiation portals were such that the major salivary glands (parotid and submandibular) were included. Radical resection or de bulking of the primary tumor often preceded the course of irradiation.

Along with radiotherapy, anticancer drugs such as 100mg/m^2 of cisplatin was given on the first day followed by the second dose on the twenty second day and third on the forty third day and 600mg/m^2 of 5-fluorouracil was administered continuously for first five days on weeks one and six respectively (Intravenously).

Mouth Washes:

The effect of three test mouthwashes and a control were assessed in the present study. The mouthwashes assessed were:

1. 0:12% chlorhexidine
2. Salt / sodium bicarbonate
3. 'magic' mouthwash
4. Plain water [control]

Other ingredients like coloring agents, sweeteners, flavouring agents were added to the mouthwash so that all of them have identical colour and acceptable taste. All the mouthwashes were alcohol – free and were prepared at

Mankind Pharma, New Delhi-20. The mouthwashes were numbered randomly from 1 to 60 by the mouth wash manufacture.

The coding was done by the manufacturer and the four different solutions were known only to him. It was later deciphered to the investigator at the end of the study.

The compositions of the dispended mouthwashes were as follows:

0.12% chlorhexidine mouthwash

Chlorhexidine gluconate	0.12%
Sodium lauryl sulphate	0.1%
Water	100%
Amaranth red	QS
Saccharin	QS

Salt / Sodium bicarbonate mouthwash

Sodium Chloride	0.4%
Sodium bicarbonate	1%
Sodium lauryl sulphate	0.1%
Water	100%
Amaranth red	QS
Saccharin	QS

"Magic"mouth wash

Lignocaine solution	0.5%
Diphenhydramine hydrochloride	0.0132%
Aluminium hydroxide suspension	14.75 ml (Maalox)
Sodium lauryl sulphate	0.1%
Water	100%
Amaranth red	QS
Saccharin	QS

Plain water [control]

Water	100%
Amaranth red	QS
Saccharin	QS
Peppermint essence	QS

QS=Quantity Sufficient

They were dispended in identical looking 500ml coded glass bottles having a lid with marking for 10ml.

Oral Care Instructions:

All patients who participated in the study had an oral examination before initiation of chemoradiotherapy. The possible oral soft tissue reactions of their

oncologic treatment were explained as well as the expected benefits of the oral care. Informed consent was obtained from the patients.

Patient Grouping:

60 patients, who met with the inclusion /exclusion criteria were selected for the study and were randomly assigned to one of the four groups. The patients were numbered 1 to 60 randomly. The patient who was assigned a particular number was also given the same numbered mouthwash. Once the mouthwash was over it was replaced with the same numbered mouthwash.

The patients were instructed to rinse 10ml [measured by marking in the lid] of the mouthwash, twice a day (morning and night after brushing) for a period of 6 weeks. They were asked to swish the mouthwash for about 2minutes and then expectorate. They were requested to do the above, after food and to abstain from eating and gargling the mouth for half an hour after use of mouthwash. The patients were initially dispended a 500ml bottle and a second bottle was given after third week.

Patient compliance was assessed with regard to the regular usage of mouthwash by checking the level of mouthwash left in the bottle provided to determine whether the mouthwash had been used regularly or not used due to certain reasons such as the taste, odour during the weekly assessments.

Assessment of Mucositis:

Mucositis was assessed using the World Health Organization grading of Mucositis, as it is the most common scale used to assess Mucositis severity. The oral cavity was divided into 8 distinguishable areas: buccal mucosa [left and right], soft and hard palate, dorsum and border of the tongue [left and right] and the floor of the mouth. Mucositis score of maximally affected area is recorded.

The WHO grading of Mucositis is as follows:

Grade 0	No symptom.
Grade 1	Soreness and erythema.
Grade 2	Erythema, ulcers; can eat solid foods.
Grade 3	Ulcers, requires liquid diet only.
Grade 4	No possible alimentation.

This scoring system includes objective changes (erthema, ulceration), subjective symptoms (pain) and functional consequences (dysphagia). The later two were assessed by questioning the patient.

Assessment of Mucositis was done at base line, and after each week of chemo radiation therapy [6 weeks]. Examinations of patients were done under standard illumination.

The following armamentarium was used for examination of patients:

1. Gloves and mouth masks
2. Mouth mirror
3. Tweezer
4. Sterile gauze pieces
5. Kidney tray, to place the instruments.
6. Tongue depressor
7. Laryngoscope

The patients were examined using proper aseptic measures and only sterile instruments were used for examination. All Patients who participated in this study were assigned separate files [which consisted of inclusion/exclusion form, informed consent -recording form] for ease maintenance of data.

Calibration of the Examiner:

Calibration of examiner in WHO grading of oral Mucositis was done before the start of the study. The assessments done by the examiner before and during the study were monitored by the staff that was not a part of the study. After completion of the study, the code of the mouthwashes was broken. The results were tabulated and statistically analyzed.

Statistical Analysis:

The results were analyzed using SPSS for windows version 10.0. The null hypothesis for the current study was that there would not be any difference

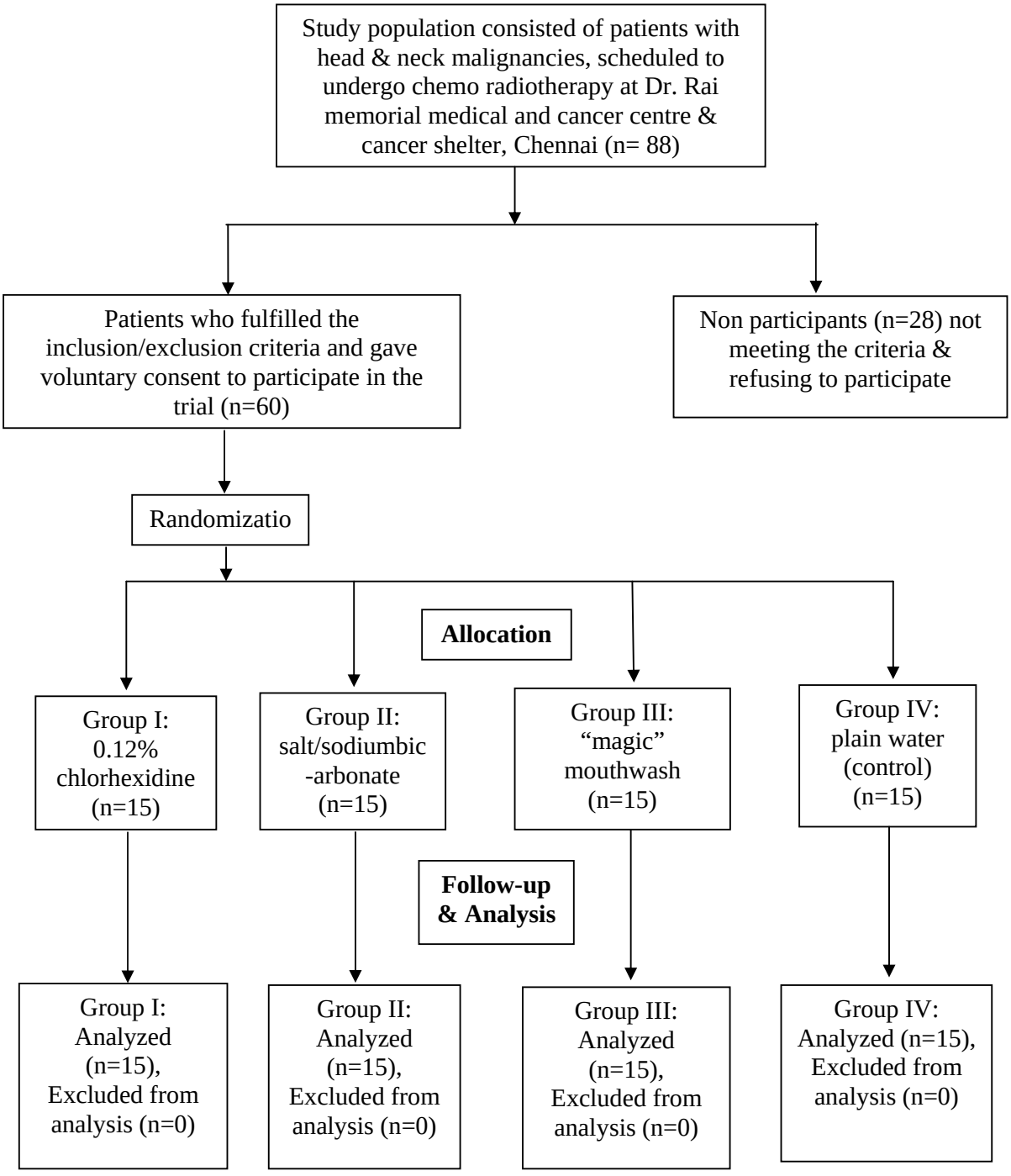
between the test groups and the control in the onset and severity of chemo radiation-induced oral mucositis in patients with head and neck malignancies. The primary endpoint of the study was to dtrmin mucositis at the end of the sixth week, after the termination of chemo radiotherapy for patients with head and neck malignancies.

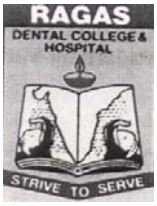
Further, the present trial was designed to have a power of 90% and alpha level of significance (type 1 error) was fixed as 0.05, i.e., the null hypothesis was rejected if the p value was less than this value. The standard difference in the mean mucositis scores between the test and the control arms was assumed from an earlier study as 1.14. However, the standard difference in the mean mucositis scores between the test arms was considered negligible in the present study. Lehr's formula was used to calculate the sample size for the power of 90% and a two-sided significance level of 0.05.

The baseline demography of the four groups was matched for age, sex, stage of cancer and whether patients had cancer of oral or extra-oral region. The former was assessed using ANOVA while the rest were analyzed using Chi-square test.

A post hoc test for repeated measures was used to find the difference of mean Mucositis scores between the groups at various week intervals.

STUDY OUTLINE





RAGAS DENTAL COLLEGE & HOSPITAL

2/102, EAST COAST ROAD, Uthandi, Chennai – 600119

DEPARTMENT OF ORAL MEDICINE & RADIOLOGY

PROFORMA FOR STUDY TO COMPARE THE EFFICACY & EFFECTIVENESS OF THREE COMMONLY USED MOUTHWASHES TO TREAT CHEMORADIOTHERAPY INDUCED MUCOSITIS

Date:

S.No:

Op.No:

Name: **Age/Sex:**

Address:

Phone number:

Occupation:

Monthly income:

Chief complaint:

History of presenting illness:

Past medical history:

Past surgical history:

Past dental history:

Personal habits:

- **Chewing habits (Duration/ Frequency)**
- **Smoking (Duration / Frequency)**
- **Alcohol consumption (Duration / Frequency)**

General examination:

- **Height / Weight: /**

Local examination:

- **Extra oral (Examination of lymph nodes)**
  - **Number of nodes**
  - **Consistency**
  - **Warmth**
  - **Tenderness**
  - **Mobile / Fixed**

- **Intra oral**

  Gingival

  Labial & buccal mucosa

  Alveolar mucosa

  Tongue

  Palatal mucosa

  Floor of the mouth

  Teeth

Diagnosis:

TNM stage: Stage I

Stage II

Stage III

Stage IV

Chemotherapy prescription:

Radiotherapy prescription: ____ Gy in _____ # in _____ weeks

Radiotherapy delivered with: Telecobalt / Linac

Mouthwash: bottle number -

Any side effect perceived:

Protocol completed: yes / no

Subjective symptoms: Pain (I / II / III / IV / V / VI weeks)

Dysphagia (I / II / III / IV / V / VI weeks)

WHO index for grading chemo radiation- induced oral mucositis

	Baseline	1st week	2nd week	3rd week	4th week	5th week	6th week
Buccal Mucosa (R)							
Buccal Mucosa (L)							
Soft Palate							
Hard Palate							
Dorsum of Tongue							
Lateral Border of tongue(R)							
Lateral Border of tongue(L)							
Floor of Mouth							
Score							

CONSENT FORM

I, _____ , the undersigned hereby give my consent for participation as a subject in the study titled "TO COMPARE THE EFFICACY AND EFFECIENCY OF THREE COMMONLY USED MOUTHWASHES TO TREAT CHEMORADIOTHERAPY INDUCED MUCOSITIS" conducted by Dr. P. Jagathesh under the guidance of Capt. Dr. S. Elangovan. Professor, Dept. of Oral Medicine & Radiology, Ragas Dental College & Hospital, Chennai.

I have been counseled about this study and as a part of this study protocol I unconditionally and freely give my consent to participate in this study.

Date:

Place:

Signature

Of the total 88 patients who reported to Dr. Rai memorial medical and cancer centre and cancer shelter for treatment of head and neck malignancies, 60 patients, who fulfilled the inclusion criteria, participated in this trial and were Randomly allocated into four groups.

Table – I: Distribution based on number of patients who completed the study in each group

The study group consisted of a total number of 60 patients who completed the study. Out of the 60 patients, 15 patients were randomly divided into four groups of 15 each. 15 patients in chlorhexidine group, 15 patients in salt/sodium bicarbonate group, 15 in "magic" mouthwash group and 15 as control group.

Table – II: Distribution of patients in Chlorhexidine group

In the chlorhexidine group the males predominated than the females with the ratio of 17:3. The most commonly seen type of cancer was cancer of the tongue (3) all being males with the age of 45, 56 and 57 followed by cancer of the buccal mucosa (2) and both being males of age 51 and 61, tonsil(2) in which 1 being a male at the age of 72 and a female at the age of 61, pyriform fossa (2) and both were males of age 55 and 63, and alveolus which consisted of males of age 56 and 61 (2) followed by the cancer of the epiglottis (1) who was a male of 58 years of age, a male of 49 years had cancer of the oropharynx (1), a female of 52 years had cancer of the nasal cavity (1) and a male of age 49 with cancer of maxillary antrum (1).

Table – III: Distribution of patients in Salt/Sodium bicarbonate group

In the salt/sodium bicarbonate group the males predominated than the females with the ratio of 17:3. The most commonly seen type of cancer was cancer of the tongue (6) among them 5 being males with the age of 48, 54, 58, 64 and 71 and 1 being a female of 51years followed by cancer of the buccal mucosa (2) and both being males of age 61 and 69, tonsil(2) both being males at the age of 48 and 64, pyriform fossa (1), a male of 39 years followed by the cancer of the epiglottis (1) who was a male of 52 years of age, a male of 59 years had cancer of the larynx (1), a female of 67 years had cancer of the vocal cords (1) and a female of age 49 with cancer of the posterior pharyngeal wall (1).

Table – IV: Distribution of patients in "magic" mouthwash group

In the "magic" mouthwash group the males predominated than the females with the ratio of 16:4. The most commonly seen type of cancer was cancer of the tongue (3) 2 being males with the age of 52 and 62 and 1 being a female of age 43 and tonsil (3) all being males of age 41,53 and 61followed by the cancer of the buccal mucosa (2) and both being a males of age 56 and 73, pyriform fossa (2) and both were males of age 49 and 69 followed by the cancer of the epiglottis (1) who was a male of 70 years of age, and alveolus which consisted of a female of age 58 (1) a male of 48 years had cancer of the oropharynx (1), a female of 71 years had cancer of the supra glottis (1) and a female of age 59 with cancer of hypopharynx (1).

Table – V: Distribution of patients in Control group

In the control group the males predominated than the females with the ratio of 15:5. The most commonly seen type of cancer was cancer of the tongue (4) 2 being males with the age of 54 and 60 and 2 being females of age 58 and 67 followed by cancer of the buccal mucosa (3) 2 being males of age 49 and 59 and females of age 41, tonsil(2) in which both being males at the age of 43 and 65 followed by cancer of pyriform fossa (1) who was a male of age 71, and alveolus(1) which consisted of a male of age 55 followed by the cancer of the epiglottis (1) who was a female of 50 years of age, a male of 69 years had cancer of the supraglottis (1), a female of 61 years had cancer of the posterior pharyngeal wall (1) and a male of age 58 with cancer of maxillary antrum (1).

Table – VI: Distribution of patients in the four groups based on sex

In all the groups, the number of males exceeded the females. Maximum number of males was present in chlorhexidine and salt/sodium bicarbonate group [80%] and control group had the minimum [66.6%]. The number of males in "magic" mouthwash group was [73.3%]. There existed no statistically significant difference between the groups based on sex distribution with **p value 0.122**.

Table – VII: Distribution of patients in the four groups based on age

The mean age of patients in chlorhexidine and salt/sodium bicarbonate group were 56.93 and ranged between 45 - 72 and 48-71 years respectively. The mean age of patients in "magic" mouthwash group was 57.66 which ranged between 41-71 years and 57.73 was the mean age of patients in

control group, ranged between 41-71 years. The overall mean age of the patients who completed the study was 57.32 and range between 41-72 years. Using ANOVA test, it was found that there existed no statistically significant difference between the age of patients in four groups with **p value 0.569**.

Table – VIII: Distribution of patients in the four groups based on the location of cancer

Cancer of tongue [26.67%] was the most common diagnosis among the patient, followed by cancer of buccal mucosa and tonsil [15%]. Other locations of cancer include the alveolus, epiglottis [6.67%], hypo pharynx, larynx, nasal cavity & vocal cords [1.67%], oropharynx, posterior pharyngeal wall, maxillary antrum & supraglottis [3.33%] and pyriform fossa [10%].

Table – IX: Distribution of patients in the four groups based on cancer of oral cavity or extra-oral region

For better understanding the patients in the four groups were divided into those cancers of oral cavity and those having cancer of extra-oral region. Cancer of extra-oral region was all the groups and accounted for 31cases, among the total completed cases. It was maximum in the “magic” mouthwash group [09], followed by chlorhexidine [08] and salt/sodium bicarbonate and control groups [07 each]. Among the 29 patients who had cancer of oral cavity, maximum belonged to salt/sodium bicarbonate and control groups [08 each], 07 in chlorhexidine group followed by the “magic” mouthwash group [06]. No statistically significant difference was found between the groups based on the location of cancer with **p value 0.688**.

Table – X: Distribution of patients in the four groups based on stage of cancer:

The patients were also grouped based on the staging of cancer, according to TNM classification. Among the total patients, 31 had stage IV cancer and 29 had stage III cancer. Maximum cases of stage III were seen in "magic" mouthwash and control groups [8 each] followed by chlorhexidine group [7] and the least was in salt/sodium bicarbonate group [6] and in stage IV the maximum number of cases were seen in salt/sodium bicarbonate group [9] followed by chlorhexidine group [8] and the least were in "magic" mouthwash group and the control groups [7 each]. Again no statistically significant was observed between the groups based on the stage of cancer with **p value 0.895**.

Thus it was found that there existed no statistically significant difference between the patients in four groups, at baseline, based on age, sex location of cancer and stage of cancer.

Table – XI: Distribution of patients in the four groups based on mean mucositis score at weekly intervals

The distribution based on the mean mucositis was more at weekly intervals, over the 6 week study period, among the four groups were compared. Though the mean mucositis score was 0 in all the groups at baseline, after the 1st week, maximum increase [0.85] was seen in the control group, while it was less in "magic" mouthwash group.

This trend continued throughout the study period. In the chlorhexidine group, the mean mucositis score increased from 0.50 at end of 1st week to 2.42 at

the end of 6th week. The mean mucositis score 1st and 6th week interval was 0.53 to 2.50 in salt / soda group. The increase in "magic" mouthwash group was from 0.30 to 1.84 and 0.85 to 2.90 in the control group. Overall the mucositis increased from 0.54 at the end of first week to 2.42 at the end of sixth week. When ANOVA test was used, a statistically significant difference was found between the groups at all the weekly intervals. The **p value at the end of 1st week was 0.014 and 0.000 at the end of 2nd, 3rd, 4th, 5th & 6th weeks** respectively.

Table – XII: Post hoc analysis of difference in mean mucositis scores between different study groups

A test of repeated measures was used to analyze the difference between the groups based on mean mucositis scores, at weekly intervals. Though there existed no difference between the groups at baseline, after the 1st week, a statistically significant difference was observed between the "magic" mouthwash group and control group with a **p value of 0.013**. At the end of second week, in addition to "magic" mouthwash group, chlorhexidine and salt/sodium bicarbonate groups also differed from the control group and were **statistically significant** with **p value of 0.000, 0.001 and 0.021 respectively**. However, there existed no significant difference between the test groups. Similar results were observed after the 3rd week, it was found that there was a significant difference between the test groups and the control group with **p value of 0.000** for "magic" mouthwash group, **0.000** for chlorhexidine group and **0.001** for salt/sodium bicarbonate group. But there existed no significant difference among the test groups.

During the end of 4th week, there was a significant difference compared to the test groups ("magic" mouthwash group, chlorhexidine and salt/sodium bicarbonate groups) and the control groups with **p value of 0.000, 0.000 & 0.002** respectively. There was also a significant difference observed between "magic" mouthwash and salt/sodium bicarbonate group with the **p value of 0.016**. 5th week values showed a significant difference not only between all the test groups ("magic" mouthwash group, chlorhexidine and salt/sodium bicarbonate groups) and control with **p value of 0.000, 0.014 & 0.018** respectively, but also within the test groups. Difference in mean mucositis scores between "magic" mouthwash and chlorhexidine groups was significantly different with a **p value of 0.037**, in addition to the difference between "magic" mouthwash and salt/soda groups with **p value of 0.037**. Values after 6th week showed a slightly different trend. Though there existed a significant difference between "magic" mouthwash and all other groups with **p value of 0.022** with chlorhexidine group, **0.007** with salt/sodium bicarbonate group and **0.000** with the control group, the difference in mean mucositis scores among other groups were **not statistically significant** with **p value of 0.085** for the chlorhexidine group & **0.252** for the salt/sodium bicarbonate group.

Table – XIII: Distribution based on the onset of mucositis between patients in the four groups

Among the 30 patients who had mucositis onset at 1st week, 12 belonged to control group while 5 belonged to "magic" mouthwash group, 7 belonged to the salt/sodium bicarbonate group and 6 belonged to the chlorhexidine group. 4 patients in "magic" mouthwash group and 5 in salt/sodium

bicarbonate group, 9 in chlorhexidine group and 3 in the control group had onset of mucositis at the end of 2nd week and 4 patients in the "magic" mouthwash group and 3 in salt/sodium bicarbonate had onset of mucositis after 3 weeks. 1 in "magic" mouthwash group had onset of mucositis at 4th and 5th weeks respectively. A Chi-square analysis showed a statistically significant difference between onset mucositis among the groups **[p = 0.005**].

Analysis was also done comparing the onset of mucositis among the test groups and control group and between the tests groups

Table - XIV: Distribution based on the onset of mucositis between patients in chlorhexidine and control groups

80% (12) of patients in control group developed mucositis at the 1st week compared to 40% (6) in chlorhexidine group and at the end of 2nd week 9 (60%) belonged to chlorhexidine group and 3(20%) belonged to control group. A **significant difference** was found between them (X^2 = 7.033, **p = 0.008**).

Table – XV: Distribution based on the onset of mucositis between patients in salt/sodium bicarbonate and control groups

The difference observed between salt/sodium bicarbonate and control group **[p = 0.05**] was **statistically significant** were the onset of mucositis was only 46.67% (7) In the salt/sodium bicarbonate group as compared to 80% (12) in control group at the end of 1st week and 5 (33.3%) for the salt/sodium bicarbonate group and 3(20%) for control group at the end of 2nd week and 3(20%) for the salt/sodium bicarbonate at the end of 3rd week.

Table – XVI: Distribution based on the onset of mucositis between patients in "magic" mouthwash and control groups

The onset of mucositis was also **statistically significant difference** between "magic mouthwash" and control group, **[p = .010]** were only 33.33% (5) of patients had onset of mucositis at 1st week in "magic" mouthwash group as compared to 80% (12) of control group. At the end of 2nd week the onset of mucositis in "magic" mouthwash it was 4(26.67%) and 3(20%) in the control group. 4 patients in the "magic" mouthwash group had onset of mucositis after 3 weeks. 1 in "magic" mouthwash group had onset of mucositis at 4th and 5th weeks respectively.

Table – XVII: Distribution based on the onset of mucositis between patients in chlorhexidine and salt/sodium bicarbonate groups

A comparison was made between chlorhexidine group and salt/sodium bicarbonate group based on the onset of mucositis. At the end of 1st week the chlorhexidine group had 6(40%) and 7 (46.67%) in the salt/sodium bicarbonate group with onset of mucositis. 9(60%) of patients in the chlorhexidine group had onset of mucositis at the end of 2nd week as compared to 5(33.3%) in the salt/sodium bicarbonate group. In the third week the salt/sodium bicarbonate group had 3(20%) patients with the onset of mucositis. There was **no significant difference** between the two groups. The **p value was 0.501** showing that there no difference in the onset of mucositis among the two groups

Table – XVIII: Distribution based on the onset of mucositis between patients in chlorhexidine and "magic" mouthwash groups

A comparison was made between the chlorhexidine group and "magic" mouthwash group based on the onset of mucositis. It was found that 6(40%) of patients had onset of mucositis compared to 5(33.3%) in "magic" mouthwash group at the end of 1st week. At the end of 2nd week the onset of mucositis in chlorhexidine group was 9(60%) as compared to 4(26.6%) in the "magic" mouthwash group. At the end of 3rd week the chlorhexidine group had 4(26.67%) of patients had onset of mucositis. 1 (6.67%) patient each had the onset of mucositis at the end of 5th and 6th weeks respectively. There was a **statistically significant** difference between the two groups. The **p value was 0.05**. "Magic" mouthwash group had statistically significant lower mucositis scores in this prospective study.

Table – XIX: Distribution based on the onset of mucositis between patients in salt/sodium bicarbonate groups

A comparison was made between the salt/sodium bicarbonate group and "magic" mouthwash group based on the onset of mucositis. At the end of 1st week the salt/sodium bicarbonate group the onset of mucositis was seen in 7(46.67%) as compared to 5 (33.3%) in the "magic" mouthwash group. At the end of 2nd week in the salt/sodium bicarbonate group 5(33.3%) and 4(26.67%) in the "magic" mouthwash had onset of mucositis. At the end of 3rd week 3(20%) in the salt/sodium bicarbonate group and 4(26.67%) had onset of mucositis. 1 (6.67%) patient each had the onset of mucositis at the end of 5th and 6th weeks respectively. There was a **statistically significant** difference between the two groups. The **p**

value was 0.025. "Magic" mouthwash group had statistically significant lower mucositis scores in this prospective study.

Table – XX: Distribution based on the inability of patients to eat solid food in four groups

There was statistically significant difference between the control group and the experiment groups in the ability of patients to eat solid food. Chlorhexidine and salt/sodium bicarbonate groups (7 each) did not have a significant difference between them and "magic" mouthwash (10) was found to have a higher degree of the patient's ability to eat solid food as compared to other experiment groups and the least was seen in the control group (3) with the **p value of 0.001**. The relative risk of inability to take solid food was 4.0375 times less in "magic" mouthwash group when compared to control group. The Relative risks were 2.25 and 2.375, when compared to chlorhexidine and salt/ sodium bicarbonate group respectively.

Table – I: Distribution based on number of patients who completed the study in each group

Group	Number
Chlorhexidine group	15 (25%)
Salt/ sodium bicarbonate group	15 (25%)
“magic” mouth wash group	15 (25%)
Control group	15 (25%)
Total	60 (100%)

Table – II: Distribution of patients in Chlorhexidine group

Pt. No	Age	Sex	Location of cancer
1	45	M	Tongue
2	51	M	Buccal mucosa
3	56	M	Tongue
4	69	F	Tonsil
5	63	M	Pyriform fossa
6	56	M	Alveolus
7	49	M	Oropharynx
8	61	M	Buccal mucosa
9	58	M	Epiglottis
10	52	F	Nasal cavity
11	57	M	Tongue
12	49	M	Maxillary antrum
13	61	M	Alveolus
14	72	F	Tonsil
15	55	M	Pyriform fossa

Table – III: Distribution of patients in salt/sodium bicarbonate group

Pt. No	Age	Sex	Location of cancer
1	48	M	Tonsil
2	71	M	Tongue
3	49	F	Posterior pharyngeal wall
4	64	M	Tongue
5	69	M	Buccal mucosa
6	52	M	Epiglottis
7	51	F	Tongue
8	39	M	Pyriform fossa
9	59	M	Larynx
10	58	M	Tongue
11	64	M	Tonsil
12	54	M	Tongue
13	67	F	Vocal cords
14	48	M	Tongue
15	61	M	Buccal mucosa

Table – IV: Distribution of patients in "magic" mouthwash group

Pt. No	Age	Sex	Location of cancer
1	56	M	Buccal mucosa
2	48	F	Oropharynx
3	70	M	Epiglottis
4	52	M	Tongue
5	59	M	Hypopharynx
6	62	M	Tongue
7	49	M	Pyriform fossa
8	58	F	Alveolus
9	41	M	Tonsil
10	61	M	Tonsil
11	69	M	Pyriform fossa
12	71	F	Supraglottis
13	53	M	Tonsil
14	73	M	Buccal mucosa
15	43	F	Tongue

Table – V: Distribution of patients in Control group

Pt. No	Age	Sex	Location of cancer
1	61	F	Posterior pharyngeal wall
2	54	M	Tongue
3	59	M	Buccal mucosa
4	71	M	Pyriform fossa
5	65	M	Tonsil
6	67	F	Tongue
7	43	M	Tonsil
8	56	F	Epiglottis
9	60	M	Tongue
10	58	M	Maxillary antrum
11	49	M	Buccal mucosa
12	58	F	Tongue
13	41	F	Buccal mucosa
14	55	M	Alveolus
15	69	M	Supraglottis

Table – VI: Distribution of patients in the four groups based on sex

Sex	Chlorhexidine group	Salt/ Sodium bicarbonate group	"magic" mouthwash group	Control group	Total
Male	12 (80%)	12(80%)	11(73.5%)	10(66.66%)	45(75%)
Female	03(20%)	03(20%)	04(26.6%)	05(33.33%)	15(25%)
Total	15(100%)	15(100%)	15(100%)	15(100%)	60(100%)

p = 0.122 (not significant)

Table – VII: Distribution of patients in the four groups based on age

	Chlorhexidine group	Salt/Sodium bicarbonate group	"magic" mouthwash group	Control group	Total
Mean age	56.933	56.933	57.666	57.733	57.316
S.D	15.067	14.067	13.334	13.267	14.684

p = 0.569 (not significant)

Table – VIII: Distribution of patients in the four groups based on the location of cancer

Location of the cancer	Chlorhexidine group	Salt/ Sodium bicarbonate group	"magic" mouthwash group	Control group	Total
Alveolus	02 (13.3%)	-	01(6.67%)	01(6.67%)	04 (6.67%)
Buccal mucosa	02(13.3%)	02(13.3%)	02(13.3%)	03 (20%)	09(15%)
Epiglottis	01(6.67%)	01(6.67%)	01(6.67%)	01(6.67%)	04(6.67%)
Hypopharynx	-	-	01(6.67%)	-	01(1.67%)
Larynx	-	01(6.67%)	-	-	01(1.67%)
Maxillary antrum	01(6.67%)	-	-	01(6.67%)	02(3.3%)
Nasal cavity	01(6.67%)	-	-	-	01(1.67%)
Oropharynx	01(6.67%)	-	01(6.67%)	-	02 (3.3%)
Postrior pharyngeal wall	-	01(6.67%)	-	01(6.67%)	02(3.3%)
Pyriform fossa	02(13.3%)	01(6.67%)	02(13.3%)	01(6.67%)	06 (10%)
Supraglottis	-	-	01(6.67%)	01(6.67%)	02(3.3%)
Tongue	03(20%)	06 (40%)	03(20%)	04 (26.67%)	16 (26.67%)
Tonsil	02(13.3%)	02(13.3%)	03(20%)	02(13.3%)	09 (15%)
Vocal cords	-	01(6.67%)	-	-	01(1.67%)
Total	15	15	15	15	60(100%)

Table – IX: Distribution of patients in the four groups based on cancer of oral cavity or extra-oral region

Groups	Chlorhexidine group	Salt/Sodium bicarbonate group	"magic" mouthwash group	Control group	Total
Oral	07 (46.67%)	08(53.33%)	06(40%)	08(53.33%)	29(48.3%)
Extra oral	08 (53.33%)	07(46.67%)	09(60%)	07(46.67%)	31(51.67%)
Total	15 (100%)	15(100%)	15(100%)	15(100%)	60(100%)

p = 0.688 (not significant)

Table – X: Distribution of patients in the four groups based on stage of cancer

	Chlorhexidine group	Salt/Sodium bicarbonate group	"magic" mouthwash group	Control group	Total
Stage III	07(46.67%)	06(40%)	08(53.33%)	08(53.33%)	29(48.3%)
Stage IV	08(53.33%)	09(60%)	07(46.67%)	07(46.67%)	31(51.67%)
Total	15(100%)	15(100%)	15(100%)	15(100%)	60(100%)

p = 0.895 (not significant)

Table – XI: Distribution of patients in the four groups based on mean mucositis score at weekly intervals

Groups		**1st week**	**2nd week**	**3rd week**	**4th week**	**5th week**	**6th week**
Chlorhexidine group	Mean	0.50	1.05	1.40	1.79	2.16	2.42
	SD	0.61	0.22	0.50	0.42	0.60	0.61
Salt/Sodium bicarbonate group	Mean	0.53	1.22	1.50	2.00	2.17	2.50
	SD	0.61	0.65	0.71	0.69	0.62	0.51
"magic" mouthwash group	Mean	0.30	0.74	1.11	1.37	1.58	1.84
	SD	0.47	0.65	0.57	0.68	0.69	0.76
Control group	Mean	0.85	1.80	2.30	2.75	2.80	2.90
	SD	0.37	0.70	0.73	0.64	0.62	0.45
Total	Mean	0.54	1.21	1.58	1.99	2.18	2.42
	SD	0.55	0.69	0.77	0.79	0.76	0.70
F		3.793	11.442	11.804	17.263	12.112	10.434
p value		**0.014**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**

Table – XII: Post hoc analysis of difference in mean mucositis scores between different study groups

Dependent variable	Group A	Groups B	Mean difference A-B	SE	Significance (p)
Base line	Chlorhexidine group	Soda	0.00	0.00	1.000
		"m" m	0.00	0.00	1.000
		Control	0.00	0.00	1.000
	Salt/Sodium bicarbonate group	CHX	0.00	0.00	1.000
		"m" M	0.00	0.00	1.000
		Control	0.00	0.00	1.000
	"magic" mouthwash group	CHX	0.00	0.00	1.000
		Soda	0.00	0.00	1.000
		Control	0.00	0.00	1.000
	Control group	CHX	0.00	0.00	1.000
		Soda	0.00	0.00	1.000
		"m" M	0.00	0.00	1.000
1st week	Chlorhexidine group	Soda	-0.08	0.173	1.000
		"m" m	0.16	0.170	1.000
		Control	-0.38	0.168	0.170
	Salt/Sodium bicarbonate group	CHX	0.08	0.173	1.000
		"m" M	0.24	0.173	1.000
		Control	-0.29	0.171	0.170
	"magic" mouthwash group	CHX	-0.16	0.170	1.000
		Soda	-0.24	0.173	1.000
		Control	**-0.53**	**0.168**	**0.013**
	Control group	CHX	0.38	0.168	0.170
		Soda	0.29	0.171	0.531
		"m" M	**0.53**	**0.168**	**0.013**

2nd week	Chlorhexidine group	Soda	-0.17	0.194	1.000
		"m" m	0.32	0.191	0.615
		Control	-0.75	0.189	0.001
	Salt/Sodium bicarbonate group	CHX	0.17	0.194	1.000
		"m" M	0.49	0.194	0.087
		Control	-0.58	0.191	0.021
	"magic" mouthwash group	CHX	-0.32	0.191	0.615
		Soda	-0.49	0.194	0.087
		Control	**-1.06***	**0.189**	**0.000**
	Control group	**CHX**	**0.75***	**0.189**	**0.001**
		Soda	**0.58***	**0.191**	**0.021**
		"m" M	**1.06***	**0.189**	**0.000**

3rd week	Chlorhexidine group	Soda	-0.08	0.209	1.000
		"m" m	0.32	0.206	0.782
		Control	**-0.88***	**0.204**	**0.000**
	Salt/Sodium bicarbonate group	CHX	0.08	0.209	1.000
		"m" M	0.39	0.209	0.379
		Control	**-0.80***	**0.207**	**0.001**
	"magic" mouthwash group	CHX	-0.32	0.206	0.782
		Soda	-0.39	0.209	0.379
		Control	**-1.19***	**0.204**	**0.000**
	Control group	**CHX**	**0.88**	**0.204**	**0.000**
		Soda	**0.80**	**0.207**	**0.001**
		"m" M	**1.19**	**0.404**	**0.000**

4th week	Chlorhexidine group	Soda	-0.21	0.203	1.000
		"m" m	0.42	0.200	0.232
		Control	**-0.96***	**0.197**	**0.000**
	Salt/Sodium bicarbonate group	CHX	0.21	0.203	1.000
		"m" M	**0.63***	**0.203**	**0.016**
		Control	**-0.75***	**0.200**	**0.002**
	"magic" mouthwash group	CHX	-0.42	0.200	0.232
		Soda	-0.63	0.203	0.016
		Control	**-1.38***	**0.197**	**0.002**
	Control group	**CHX**	**0.96***	**0.197**	**0.000**
		Soda	**0.75***	**0.200**	**0.002**
		"m" M	**0.75***	**0.197**	**0.000**

5th week	Chlorhexidine group	Soda	-0.09	0.208	1.000
		"m" m	**0.58***	**0.205**	**0.037**
		Control	**-0.64***	**0.203**	**0.014**
	Salt/Sodium bicarbonate group	CHX	0.09	0.208	1.000
		"m" M	**0.59***	**0.208**	**0.037**
		Control	**-0.80***	**0.206**	**0.018**
	"magic" mouthwash group	**CHX**	**-0.58***	**0.205**	**0.037**
		Soda	**-0.59***	**0.208**	**0.037**
		Control	**-1.19***	**0.204**	**0.000**
	Control group	**CHX**	**0.64***	**0.203**	**0.014**
		Soda	**0.63***	**0.206**	**0.018**
		"m" M	**1.22***	**0.203**	**0.000**

6th week	Chlorhexidine group	Soda	-0.08	0.197	1.000
		"m" m	**0.58***	**0.193**	**0.022**
		Control	-0.48	0.190	0.085
	Salt/Sodium bicarbonate group	CHX	0.08	0.196	1.000
		"m" M	**0.66***	**0.196**	**0.007**
		Control	-0.40*	0.193	0.252
	"magic" mouthwash group	**CHX**	**-0.58***	**0.193**	**0.022**
		Soda	**-0.66**	**0.196**	**0.007**
		Control	**-1.06***	**0.190**	**0.000**
	Control group	CHX	0.48	0.190	0.085
		Soda	0.40	0.193	0.252
		"m" M	**1.06***	**0.190**	**0.000**

'*' = p value is statistically significant

CHX = Chlorhexidine group

Soda = Salt/Sodium bicarbonate group

"m" M = "magic" Mouthwash group

Table – XIII: Distribution based on the onset of mucositis between patients in the four groups

Weeks	Chlorhexidine group	Salt/Sodium bicarbonate group	"magic" mouthwash group	Control group	Total
1	6 (40%)	7 (46.67%)	5(33.3%)	12(80%)	30(50%)
2	9 (60%)	5(33.3%)	4(26.67%)	3(20%)	17(28.3%)
3		3(20%)	4(26.67%)		11(18.3%)
4			1(26.67%)		1(1.67%)
5			1(26.67%)		1(1.67%)
Total	15(100%)	15(100%)	15(100%)	15(100%)	60 (100%)

p = 0.0005 (highly significant)

Table - XIV: Distribution based on the onset of mucositis between patients in chlorhexidine and control groups

Week	Chlorhexidine group	Control group	Total
1	6(40%)	12(80%)	18(60%)
2	9(60%)	3(20%)	12(40%)
Total	15(100%)	15(100%)	30(100%)

p = 0.008 (highly significant)

Table – XV: Distribution based on the onset of mucositis between patients in salt/sodium bicarbonate and control groups

Week	Salt/Sodium bicarbonate group	Control group	Total
1	7(46.67%)	12(80%)	19(63.33%)
2	5(33.3%)	3(20%)	08(20.67%)
3	3(20%)		03(10%)
Total	15(100%)	15(100%)	30(100%)

p = 0.05 (significant)

Table – XVI: Distribution based on the onset of mucositis between patients in "magic" mouthwash and control groups

Week	"magic" mouthwash group	Control group	Total
1	5(33.3%)	12 (80%)	17 (56.67%)
2	4(26.67%)	3(20%)	07(23.3%)
3	4(26.67%)		04(13.3%)
4	1(6.67%)		01(3.3%)
5	1(6.67%)		01(3.3%)
Total	15(100%)	15 (100%)	30(100%)

p = 0.010 (highly significant)

Table – XVII: Distribution based on the onset of mucositis between patients in chlorhexidine and salt/sodium bicarbonate groups

Week	Chlorhexidine group	Salt/Sodium bicarbonate group	Total
1	6(40%)	7(46.67%)	19(63.3%)
2	9(60%)	5(33.3%)	08(20.67%)
3	-	3(20%)	03(10%)
Total	15(100%)	15(100%)	30(100%)

p = 0.501(not significant)

Table – XVIII: Distribution based on the onset of mucositis between patients in chlorhexidine and "magic" mouthwash groups

Week	Chlorhexidine group	"magic" mouthwash group	Total
1	6(40%)	5(33.3%)	17(56.67%)
2	9(60%)	4(26.67%)	07(23.3%)
3	-	4(26.67%)	04(13.3%)
4	-	1(6.67%)	01(3.3%)
5	-	1(6.67%)	01(3.3%)
Total	15(100%)	15(100%)	30(100%)

p = 0.05 (significant)

Table – XIX: Distribution based on the onset of mucositis between patients in salt/sodium bicarbonate and "magic" mouthwash groups

Week	Salt/sodium bicarbonate group	"magic" mouthwash group	Total
1	7(46.67%)	5(33.3%)	17(56.67%)
2	5(33.3%)	4(26.67%)	07(23.33%)
3	3(20%)	4(26.67%)	04(13.33%)
4	-	1(6.67%)	01(3.33%)
5	-	1(6.67%)	01(3.33%)
Total	15(100%)	15(100%)	30(100%)

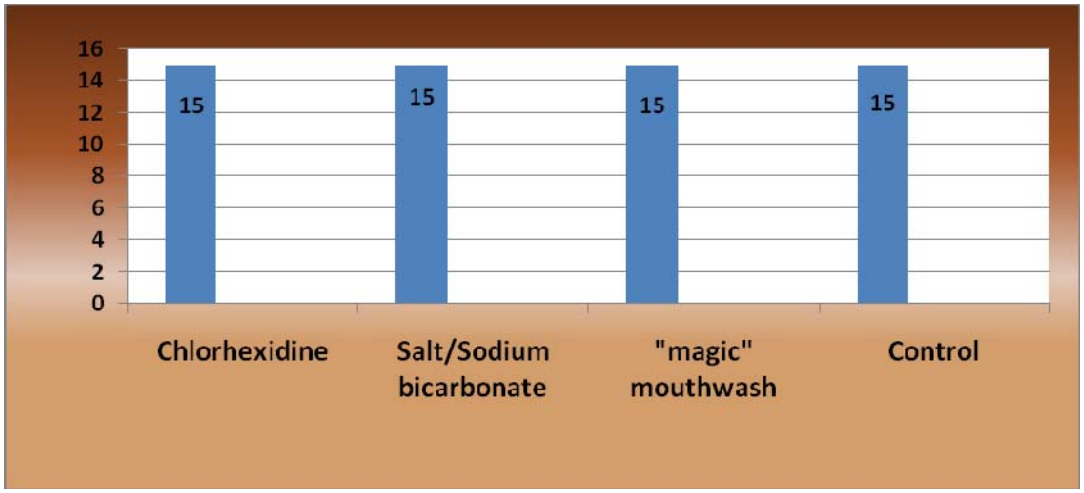
p = 0.025 (significant)

Table – XX: Distribution based on the inability of patients to eat solid food in four groups

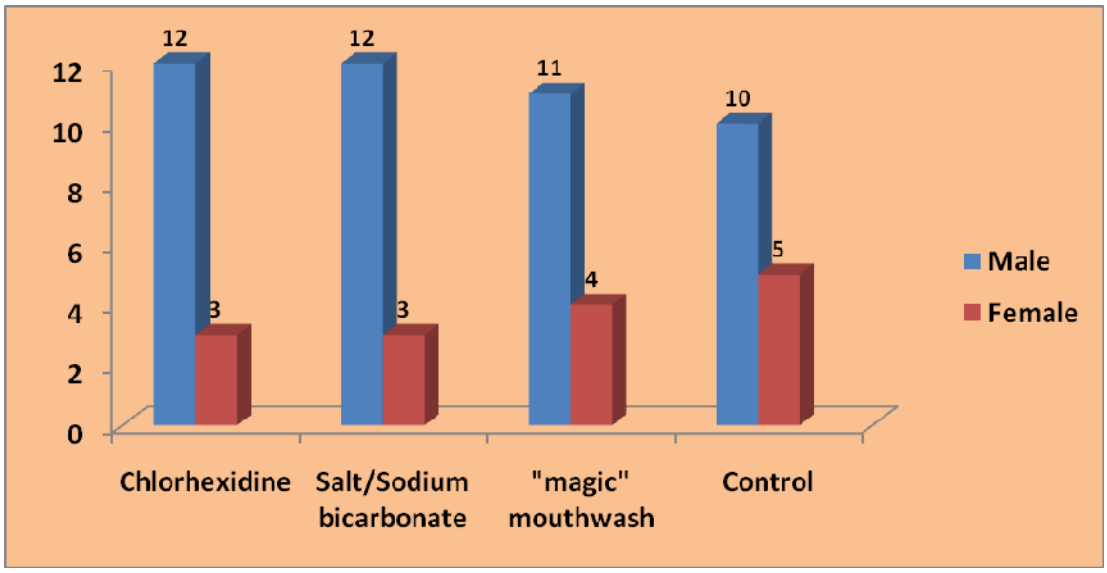
	Chlorhexidine group	Salt/sodium bicarbonate group	"magic" mouthwash group	Control group	Total
Inability to eat solid food	08(53.3%)	08(53.3%)	05(33.3%)	12(80%)	33(55%)
Ability to eat solid food	07(46.67%)	07(46.67%)	10(66.67%)	03(20%)	27(45%)
Total	15(100%)	15(100%)	15(100%)	15(100%)	60(100%)

p value of 0.001 (very highly significant)

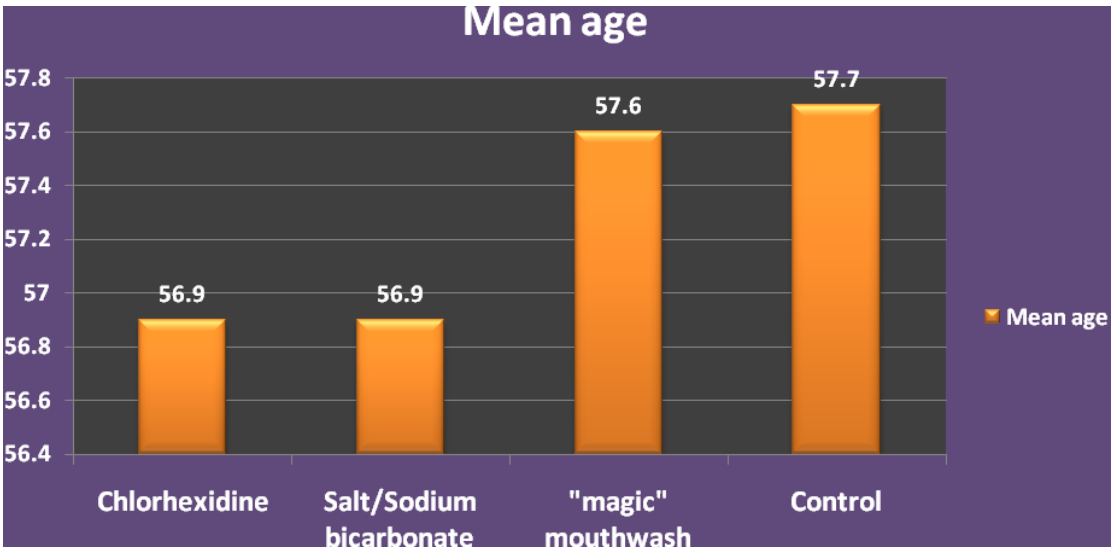
Graph – I: Distribution based on number of patients who completed the study in each group



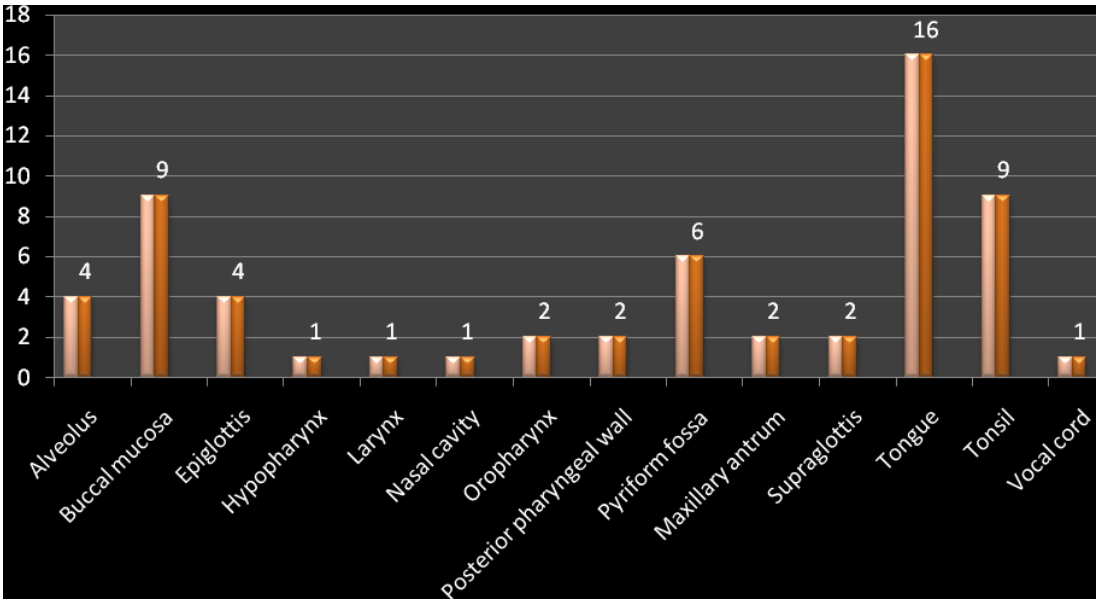
Graph – II: Distribution of patients in the four groups based on sex



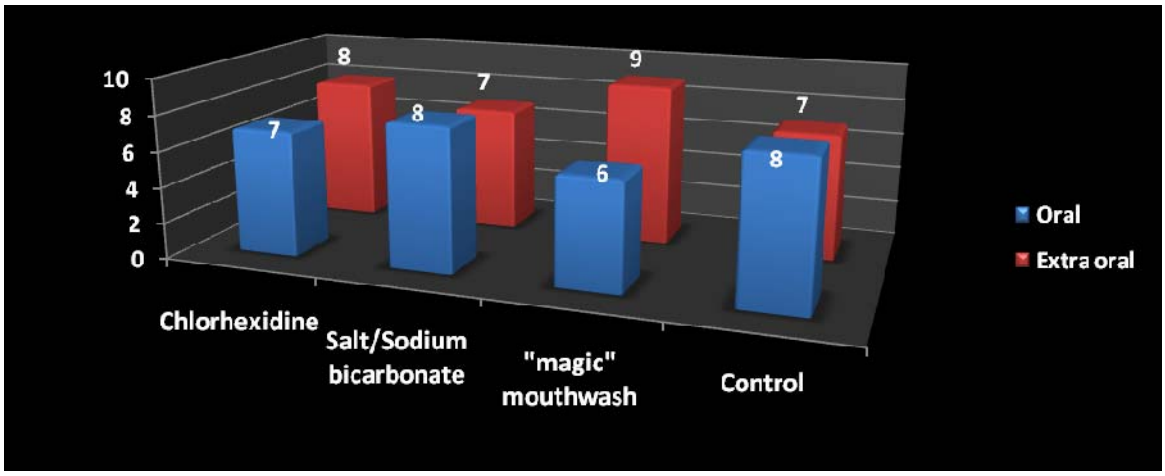
Graph - III: Distribution of patients in the four groups based on age



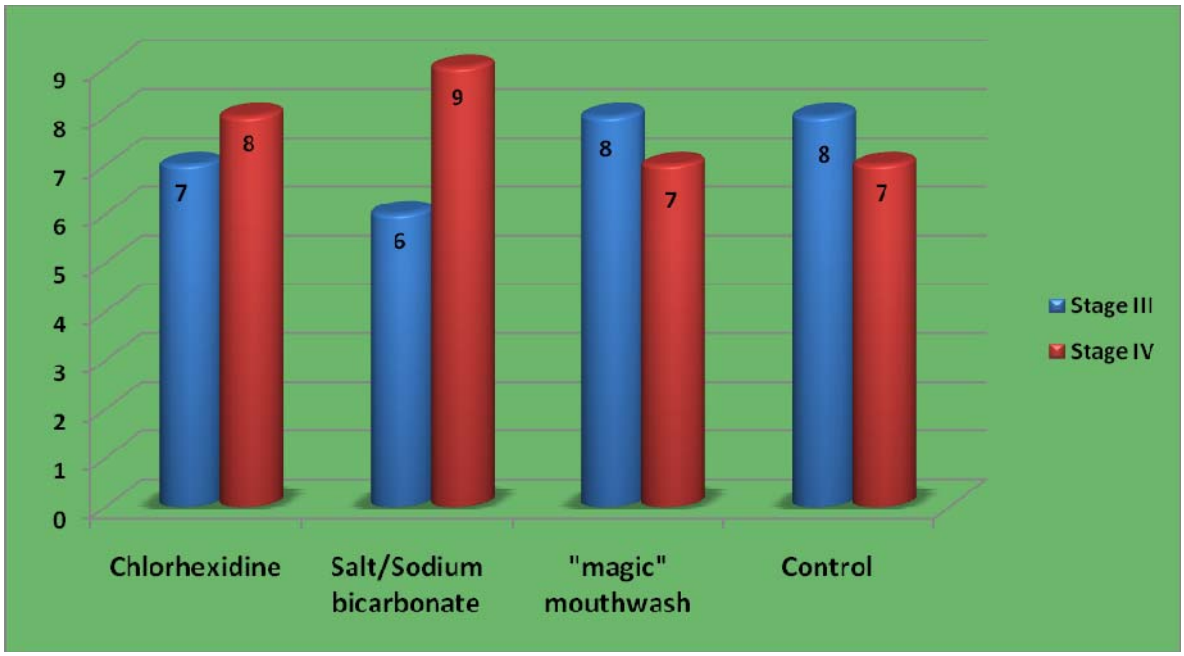
Graph – IV: Distribution of patients in the four groups based on the location of cancer



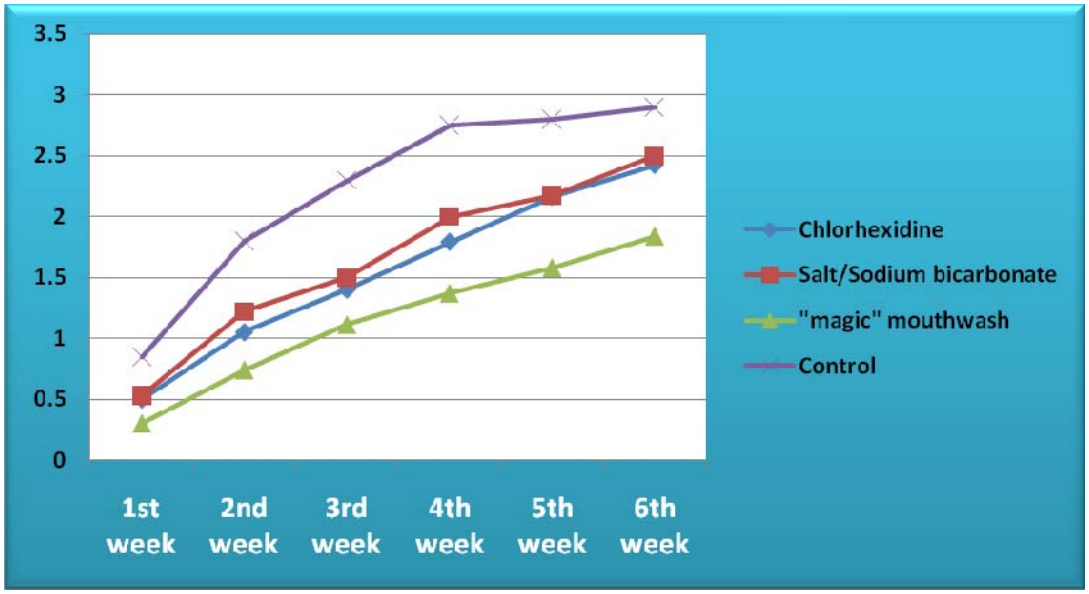
Graph – V: Distribution of patients in the four groups based on cancer of oral cavity or extra-oral region



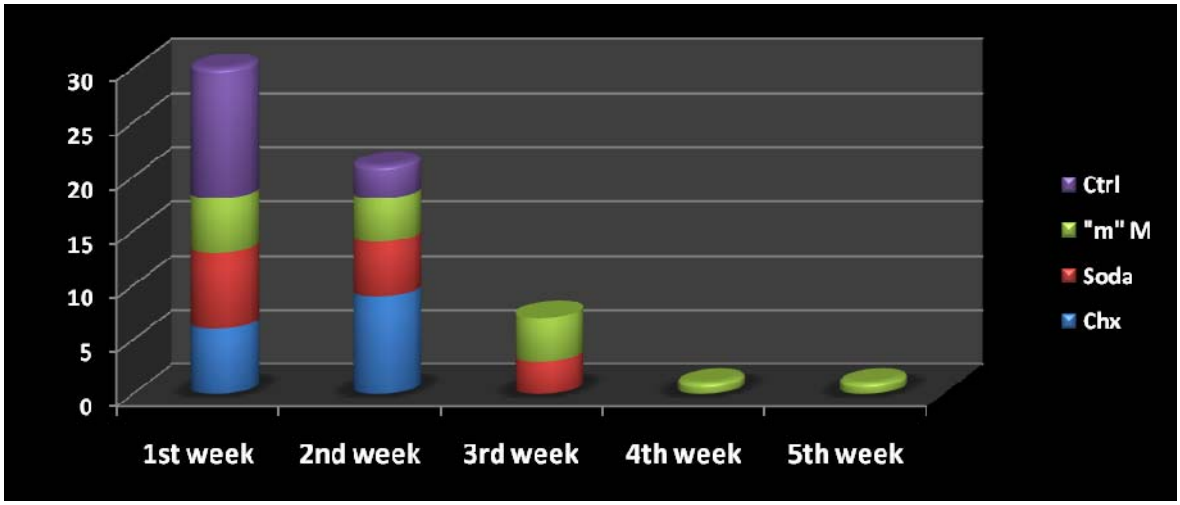
Graph – VI: Distribution of patients in the four groups based on stage of cancer



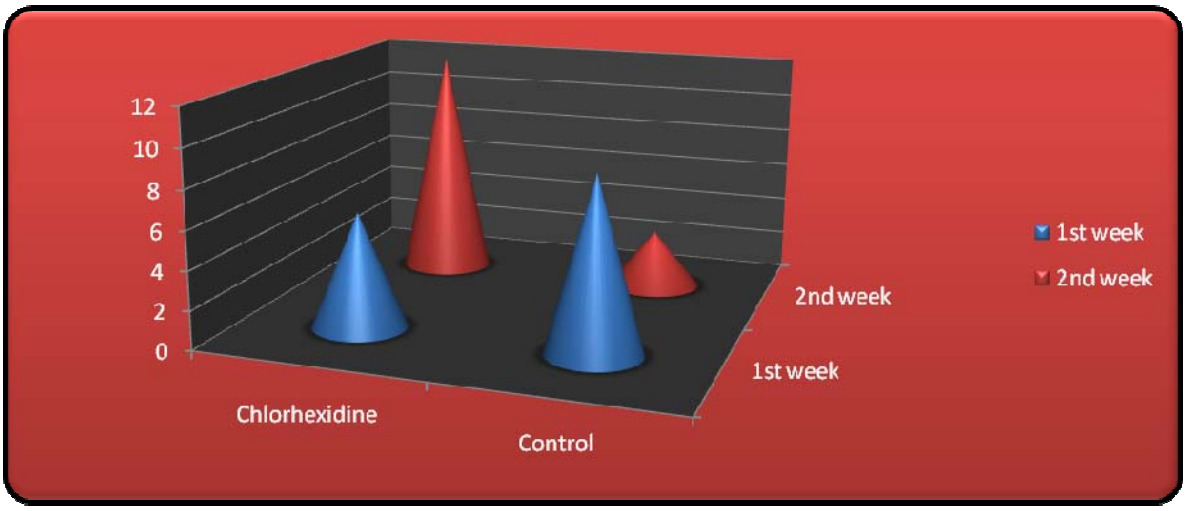
Graph – VII: Distribution of patients in the four groups based on mean mucositis score at weekly intervals



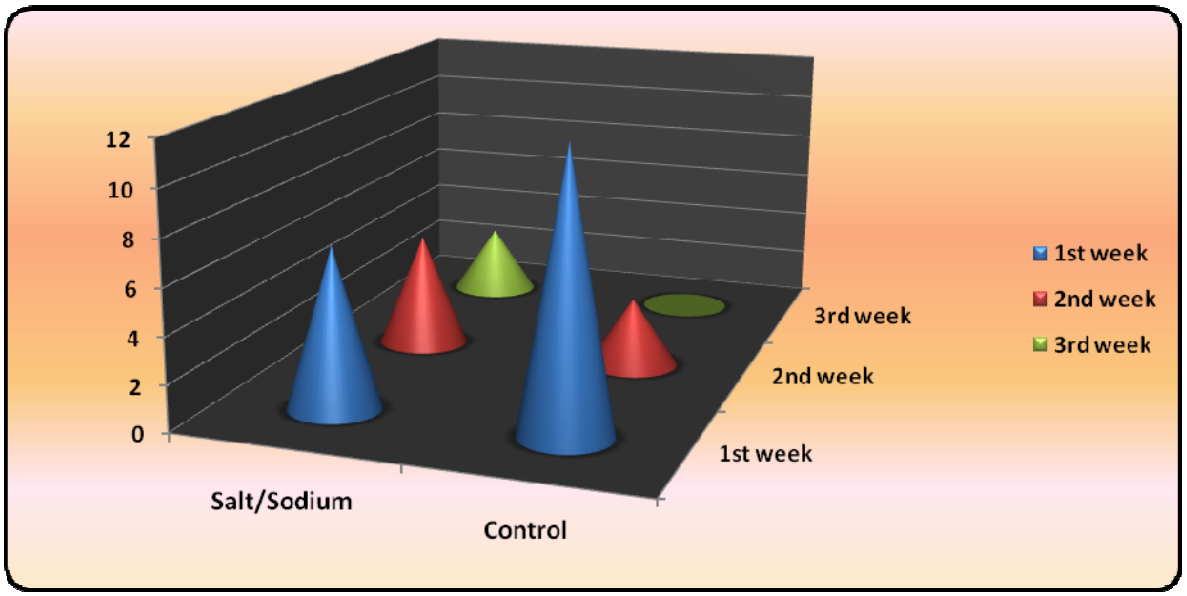
Graph – VIII: Distribution based on the onset of mucositis between patients in the four groups



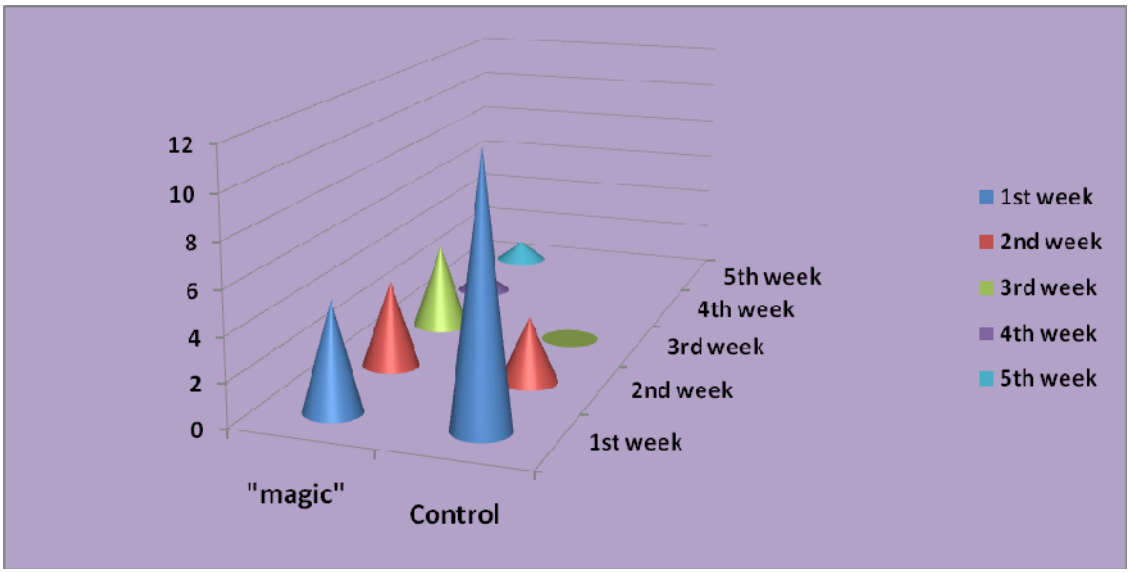
Graph - IX: Distribution based on the onset of mucositis between patients in chlorhexidine and control groups



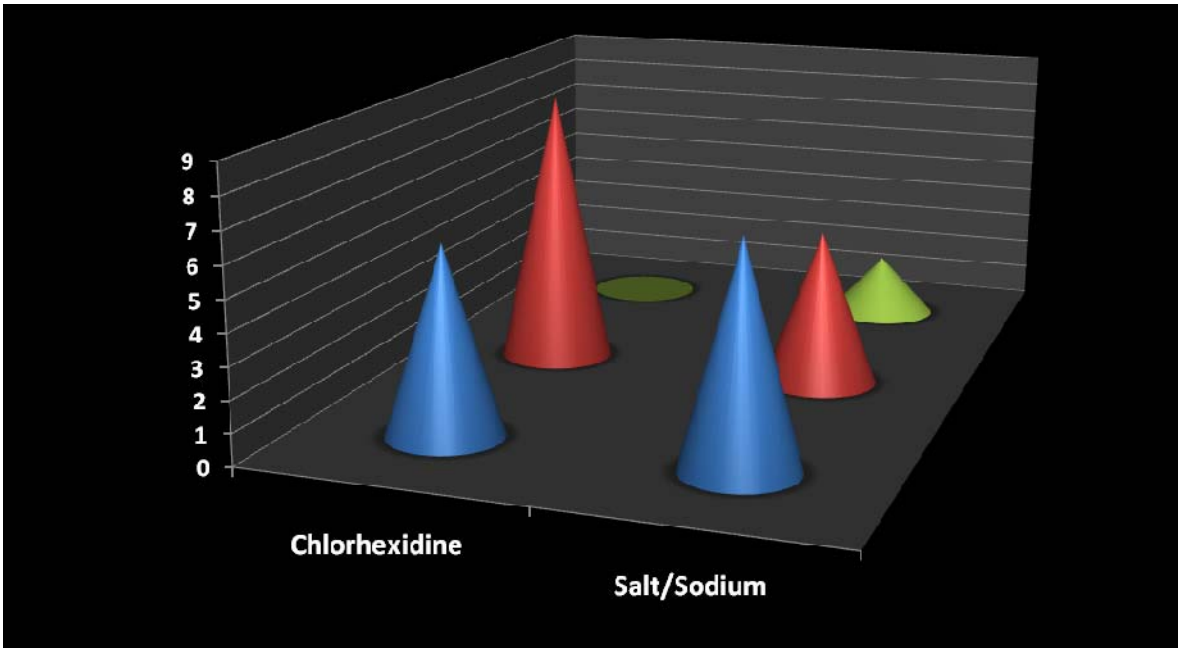
Graph – X: Distribution based on the onset of mucositis between patients in salt/sodium bicarbonate and control groups



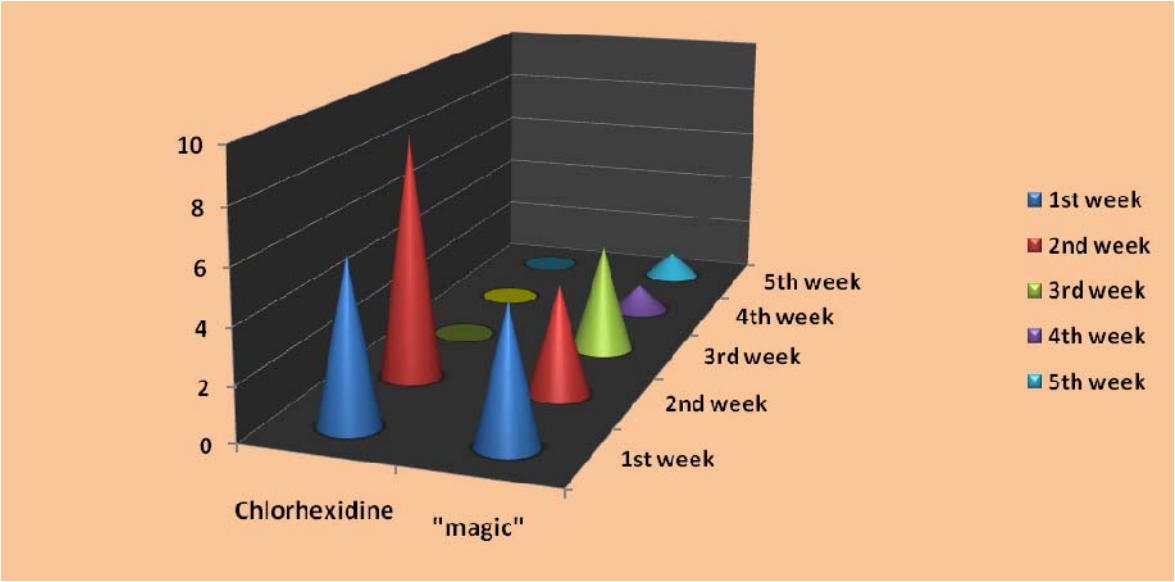
Graph – XI: Distribution based on the onset of mucositis between patients in "magic" mouthwash and control groups



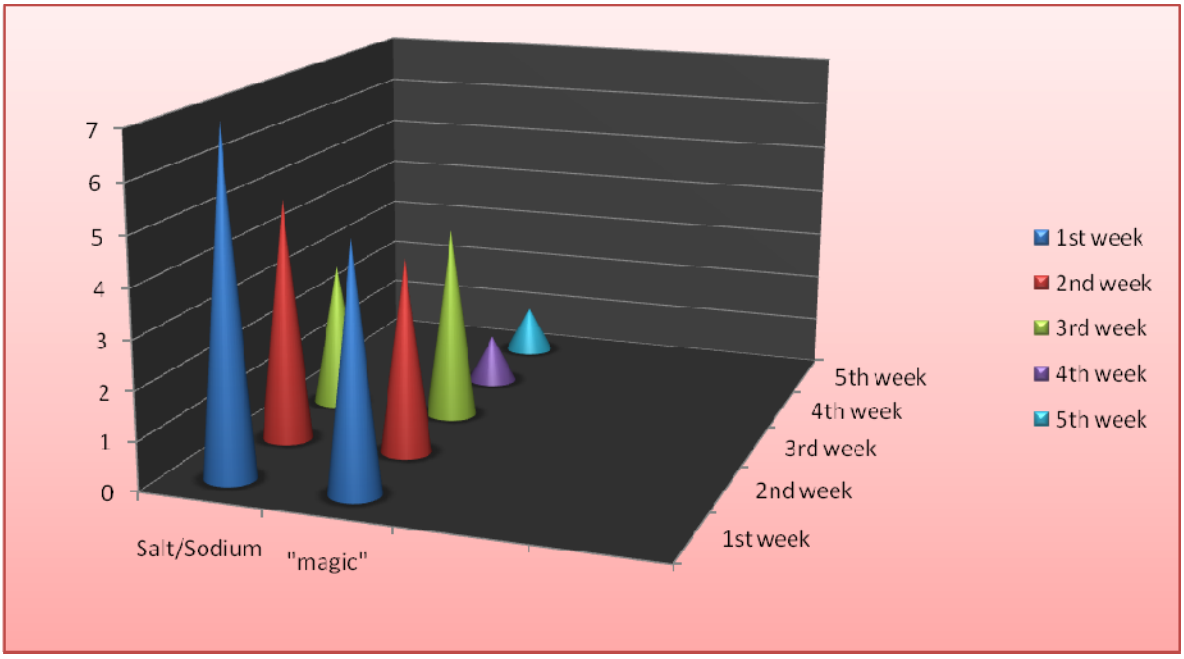
Graph – XII: Distribution based on the onset of mucositis between patients in chlorhexidine and salt/sodium bicarbonate groups



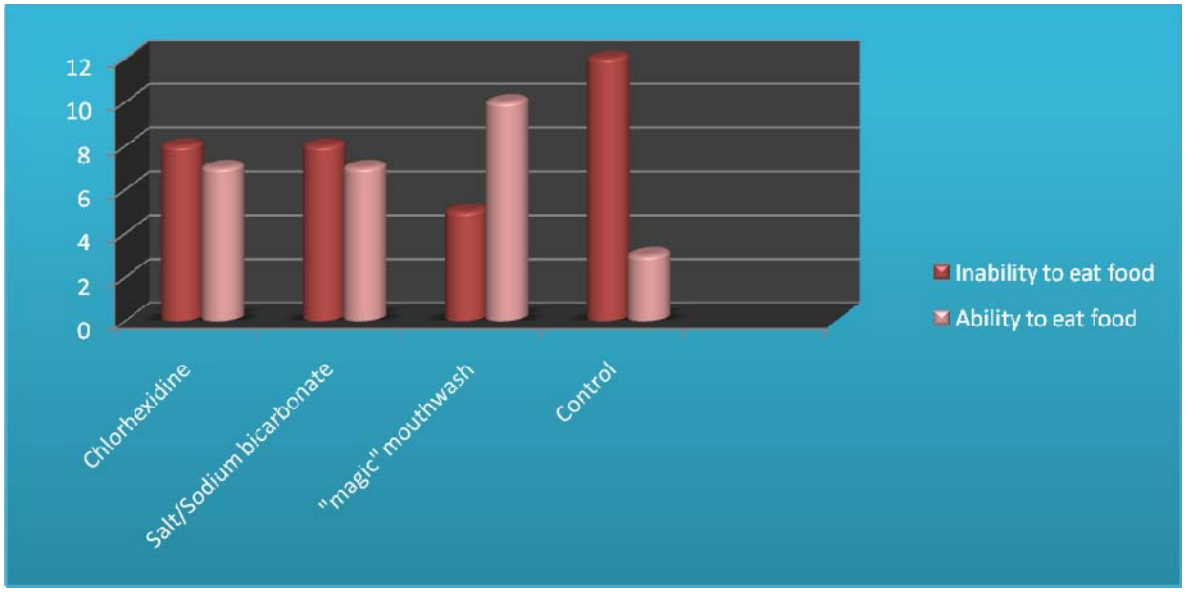
Graph – XIII: Distribution based on the onset of mucositis between patients in chlorhexidine and "magic" mouthwash groups



Graph – XIV: Distribution based on the onset of mucositis between patients in salt/sodium bicarbonate and "magic" mouthwash groups



Graph – XV: Distribution based on the inability of patients to eat solid food in four groups



Head and neck cancers rank among the top three malignancies in our country for both males and females. The wide spread use of tobacco in various forms due to our cultural habits coupled with lack of awareness of its carcinogenic effects are mainly responsible for their prevalence. Ignorance of the early symptoms together with the lack of proper diagnostic and treatment facilities at the gross root level lead to presentation of patients to cancer hospitals in advanced disease stages in our country.

Radiation/chemotherapy (combination therapy) is a unique modality of cancer treatment which can be used to cure and palliate cancer. Here high energy ionizing radiation, is made to pass through cancerous tissues, leading to ionization of the DNA (Deoxyribonucleic acid) of the later; either directly or indirectly (through free radical formation) causing reproductive death in the cancerous cells. Thus when the damaged cancerous cell attempts to divide it suffers cell death, leading to tumor regression which occurs over a period of several days i.e. up to six weeks after the completion of radiation. It has been estimated that nearly 70% of all cancers need some form of radiotherapy to complete their treatment.

One of the most important applications of combination therapy is in the treatment of head and neck cancers where combination therapy is favoured over surgery due to the functional loss associated with later. Radiation, differs from other forms of therapy in that, there are effective antidotes for side effects induced by allopathic drugs while radiation induced side effects are usually persistent, problematic, debilitating and difficult to relieve permanently. Hence preventing these side effects is of immense importance to ensure the success of treatment.

Radiation induced side effects result from the damage caused by the radiation to the normal tissues which lie in the path of the radiation beam. The effects of radiation on the normal tissues varies depending on the tissue type and its radio sensitivity, radiation dose (total dose and dose per radiation fraction), volume of normal tissue irradiated, radiation technique and equipment used and combination of other treatment modalities such as chemotherapy. Based on their severity radiation induced toxicity are graded as reactions or toxicity. While low grade radiation induced changes are called reactions whereas severe forms of the same injury are referred to as toxicity.

The aim of radiotherapy treatment planning is to maximize the dose delivery to the tumor without exceeding the normal tissue tolerance for radiotherapy. However in spite of the utmost care in preventing normal tissue reactions, one can only minimize normal tissue reactions and cannot prevent them totally. Hence emphasis in research work on radiation science is centered not only on identifying methods to improve the precision of dose delivery but also in identifying newer therapeutic modalities to cure and minimize the morbidity of radiation induced toxicity.

Radiation or chemotherapy induced mucositis is an important and inseparable side effect of head and neck radiation. Mucositis usually begins in the third week of radiation or chemotherapy and progressively increases in severity with continued treatment. Randomized controlled studies have shown that any disruption in the treatment leads to tumor repopulation which negatively affects tumor control. Attempts to minimize tumor repopulation such as accelerated

fractionation, Continuous hyper fractionated accelerated radiotherapy have increased local control at the cost of increased acute toxicity manifesting primarily as severe mucositis. The same holds good for concurrent chemo-radiation as well. Thus at every step in the treatment of head and neck malignancies the occurrence and severity of radiation induced mucositis acts as a rate limiting step, which has to be overcome to increase local control and treatment efficacy.

Currently there is no worldwide concurrence on the treatment protocol to be followed to manage radiation induced mucositis. While the broad principles of treatment such as maintenance of oral hygiene use of antibiotics and analgesics have remained the same for the past several years, oncological research is yet to identify the single drug of choice to treat / cure radiation induced mucositis.

The present study was done to find out the effect of three alcohol-free mouthwashes on chemo radiation – induced oral mucositis in patients with head and neck malignancies. It is predictable that chemo radiotherapy for head and neck malignancies will result in oral mucositis when the oral mucosa is included in the treatment field. The study of oral mucositis associated with chemo radiotherapy can serve as a model for mucosal disruptions resulting from other causes, when symptomatic management is studied. Therefore, the findings of this trial may have implications in management of mucositis as a result of causes that may include radiotherapy, chemotherapy, trauma, infection and oral dermatosea[12].

Increased risk of oral cancer among users of alcohol – containing mouthwash was observed several years ago. In one hospital-based investigation

conducted by the American Health Foundation, a significant 2.8-fold excess risk was found among women who used mouthwash daily, with the odds ratio [OR] increasing to 3.6 among non smokers and non drinkers, while the odds ratio among men was 1.1[43].

In a study by **Bolt WJ et al**[2] investigated the high risk of oral cancer among women involving 206 cancer patients and 352 controls. Odds ratio associated with alcohol-containing mouthwash use was 1.1 overall, but 1.9 among those abstaining from tobacco use.

Weaver A et al[40], in their study observed that among 11 oral cancer patients who used neither tobacco nor alcohol, 10 were long-term alcohol-containing mouthwash users.

Mashberg A et al [23] in their study showed that the use of mouthwash containing alcohol have little association with oral and pharyngeal cancer. The adjusted odds ratio of 0.94 indicated that the risk of cancer was actually slightly less for mouthwash users than for non-users.

However **Winn MD et al** [42], in his interview with 866 patients with cancer of the oral cavity and pharynx, and 1249 controls of similar age and sex, from the general population in four areas of the United States, revealed increased risks associated with the regular use of alcohol-containing mouthwash. Risk of oral cancer was elevated by 40% among males and 60% among females, after adjusting for tobacco and alcohol consumption.

Whether mouthwash use per se, or factors related to mouthwash use or its reporting, accounts for the association with oral cancer, is not clear [42]. A causal interpretation seems biologically plausible because mouthwash contains an oral carcinogen, alcohol, and drinking alcoholic beverages is a well-recognized cause of oral cancer [42]. Alcohol is generally used in mouthwashes to enhance flavor impact and also solubilize the flavor and some active ingredients, and also provide some preservative power.

Mouthwashes often contain coloring, flavoring or sweetening agents, but the association with brands having a high alcohol-content suggests that alcohol may be responsible for carcinogenesis, at least in part. Since pure alcohol [i.e., ethanol] has not been shown to be carcinogenic in laboratory animals, the mechanism by which alcoholic beverages induce oral cancer is unknown, but probably involves topical exposure, perhaps with a solvent action that enhances penetration of tobacco and other carcinogens. Oral swishing with a mouthwash containing 25% ethanol might provide a local mucosal tissue exposure similar to drinking a 100 proof (50% ethanol) alcoholic beverage diluted with equal parts of alcohol or other mixers, although quantitative comparisons are not available [42].

Recent studies [4] have shown no significant difference between alcoholic and alcohol-free formulations of chlorhexidine in reducing plaque and papillary bleeding. Hence, in the present study, the effects of three alcohol-free mouthwashes were assessed.

Chlorhexidine gluconate is the most commonly used mouthwash in dentistry. It is an antimicrobial agent that appears to be effective in controlling early periodontal infections. It reduces the oral micro flora, promote re-epithelization of soft tissue lesions, normalize the pH of oral fluids, has an acceptable taste, and it is nontoxic.

Saline solution is thought to aid in formation of granulation tissue and to promote healing. Saline solution mouthwashes are safe and economic and have been used in cancer population. Normal saline gargles cleanse the wounds, reduce swelling and can decrease pain. Sodium bicarbonate has also been used as a cleansing agent because of its ability to dissolve mucus and loosen debris. The combination of salt and sodium bicarbonate raises oral pH and prevents overgrowth of aciduric bacteria.

Recent reports suggested that the 'magic' mouthwash which consisted of "mixtures" aimed at producing analgesia or anesthesia and coating the inflamed and painful oral mucosa. There is not much evidence existing to support the efficacy of this mixture in the treatment of mucositis but this combination could be a material of choice for treating mucositis[9].

Thus, the above mentioned three mouthwashes were chosen to assess their efficacy in reducing chemo-radiotherapy induced mucositis.

The study group consisted of a total number of 60 patients; the patients were randomly and equally divided in four groups of 15 each. The four groups

were (i) chlorhexidine group, (ii) salt/sodium bicarbonate group, (iii) “magic” mouthwash group and (iv) control group.

The mean age of patients in chlorhexidine and salt/sodium bicarbonate group were 56.93 years each and the mean age of patients in “magic” mouthwash group was 57.66 years and 57.73 years was the mean age of patients in control group. It was found that there existed no statistically significant difference between the ages of patients in four groups.

In all the groups, the number of males exceeded the females. 80% of the patients were males in both chlorhexidine and salt/sodium bicarbonate group followed by 73.3% in the “magic” mouthwash group and the control group had the minimum of 66.6%. There existed no statistically significant difference between the groups based on sex distribution.

Radiation field size is always more for patients with cancer of oral cavity than those with cancer of extra-oral region. The above difference can be explained by the fact that radiation damage is site-specific; toxicity is localized to irradiated tissue volume. Hence toxicities of radiotherapy are always severe for patients with cancer of oral cavity, than the latter. Based on this report four groups were divided into those cancers of oral cavity and those having cancer of extra-oral region. Cancer of alveolus, buccal mucosa and tongue were considered as cancer of oral cavity, the rest were considered as cancer of extra-oral region. Cancer of extra-oral region was all the groups and accounted for 31(51.67%) cases, among the total completed cases and 29(48.3%) patients who had cancer of oral cavity. No

statistically significant difference was found between the groups based on the location of cancer.

The patients were also grouped based on the staging of cancer, according to TNM classification. Among the total patients, 51.67% had stage IV cancer and 48.3% had stage III cancer. Again no statistically significant was observed between the groups based on the stage of cancer.

Thus, it was found that there existed no statistically significant difference between the patients in four groups, at baseline, based on age, sex, location of cancer and stage of cancer.

The present study demonstrates that rinsing with "magic" mouthwash reduced the incidence and severity of radiation-induced oral mucositis, when compared to chlorhexidine, salt/soda and placebo mouthwash. **Dodd et al**[9] in their studies had shown that rinsing with salt/soda, chlorhexidine and "magic mouthwash produced similar results and reduced the incidence, severity and duration of chemotherapy-induced oral mucositis.

Oral mucositis during radiation therapy is caused by various factors, while pain and inability to eat are the common complaints of patients with mucositis. Therefore, analgesic or anesthetic agents may decrease the severity of pain and improve the ability to eat[31]. For this purpose, "magic" mouthwash seems to be very useful. "Magic" mouthwash forms a coating over the inflamed and painful oral mucosa. The 3 most common ingredients in these mixtures are

viscous lidocaine solution, diphenhydramine hydrochloride and aluminium hydroxide suspension. However, because the use of these agents is common in clinical practice, this combination could be a material of choice for treating mucositis[9].

Another well-known economic antiseptic agent, chlorhexidine was not found to be as effective as "magic" mouthwash in the present study. In their studies, **Spijkervet FKL et al**[32] and **Ferretti GA et al**[15] observed little or no reduction of mucositis in patients receiving high-dose head and neck radiotherapy when chlorhexidine was used as mouthwash. **Foote RL et al**[15], in his study, showed slightly more stomatitis and side effects in the chlorhexidine patients, thus ruling out the possibility that chlorhexidine can lower the average daily mucositis score. However the placebo mouthwash used in this study did not contain any alcohol while chlorhexidine had a 12% alcohol vehicle.

Epstein JB et al[12] demonstrated little effect on lactobacillus count in patients receiving cancer radiotherapy after use of chlorhexidine rinse.

The lack of effect of chlorhexidine mouthwash in patients undergoing radiotherapy may be explained by the observation that the chlorhexidine molecule, a divalent cation, probably does not bind directly to epithelial tissues but rather to negatively charged salivary mucins or glycoproteins. In-vitro evidence further supports the concept that salivary glycoproteins are necessary co-factors for mucosal cell protection by chlorhexidine. But, severe persistent xerostomia develops in patients receiving high-dose radiation therapy rather

quickly [within 14 to 21 days] after the initiation of radiation therapy, thus depriving oral epithelial tissues of their usual coating of salivary fluids, and diminishing the effect of chlorhexidine in these patients[14]. However **Toljanic JA et a1**[37], in his study on six subjects, showed that 0.12% chlorhexidine was retained in the oral cavity for atleast 4 hours after an initial rinsing, and that the property of substantivity remains active, in spite of radiation – induced changes in the oral cavity and salivary glands.

Samaranayake LP et al[29] suggested use of chlorhexidine rinse in patients undergoing post-operative radiotherapy for squamous carcinoma of oral cavity than Benzylamine mouthwash as former caused less oral discomfort.

In the present study, the effect of salt/soda mouthwash was also not as effective as "magic" mouthwash, though it was more effective than control group. **Feber T**[14], in his study, concluded that management of mucositis in oral irradiation was better with saline than hydrogen peroxide rinses. **Dodd MJ et al**[10] suggested than since there is no significant difference in efficacy between micronized sucrolfate and salt and soda, use of the less costly salt and soda is prudent and cost-effective. However **Carl W and Emrich LS**[5] showed that grade-3 mucositis developed more in patients who used conventional oral care with 5% sodium bicarbonate, saline and 3% hydrogen peroxide.

Studies have shown that frequency of mucositis was highest in patients treated with radiotherapy, affecting 100% of patient's overall[38]. In the present study also, all the patients (60 patients) who completed the trial developed some

degree of mucositis. The onset, intensity and duration of mucositis vary with the individual but most often start in the second week of therapy, or after a dose of about 2000 cGy. More than 50% patients (30), in the present trial developed mucositis in the first week after radiotherapy, while another 17 developed mucositis after 2 weeks of therapy. The range of onset of mucositis was 1-2 weeks for chlorhexidine and control group, 1-5 weeks for "magic" mouthwash and 1-3 weeks for salt/ sodium bicarbonate group. The onset of mucositis was significantly slow in "magic" mouthwash group when compared to control group and the other test groups.

The ability to take solid food [score 3 and above] was calculated between "magic" mouthwash and other groups. Among the four groups, there was statistically significant difference between the control group and the experiment groups in the ability of patients to eat solid food. Chlorhexidine and salt/sodium bicarbonate groups did not have a significant difference between them and "magic" mouthwash was found to have a higher degree of the patient's ability to eat solid food as compared to other experiment groups. The relative risk of inability to take solid food was four times less in "magic" mouthwash group when compared to control group. The relative risks were 2 each, when compared to chlorhexidine and salt/ sodium bicarbonate group respectively.

To summarize,

Just as every action has an equal and opposite reaction, every drug has its own beneficial as well as adverse effects. Radiotherapy like chemotherapy can be compared to a drug which cures cancer, but with its side effects causes debilitating effects on organs. One of the most important and debilitating effects of radiation on normal tissues, which is potentially curable, is radiation induced mucositis. It is seen as an inevitable accompaniment to external beam radiotherapy and mucositis is a painful condition which is debilitating physically and mentally.

The current randomized controlled study evaluated the effectiveness of 3 commonly used mouthwashes to treat chemo radiotherapy induced mucositis. The study was conducted in the department of Oral Medicine and Radiology, Ragas Dental College, Uthandi, Chennai at Dr. Rai memorial medical and cancer centre and cancer shelter, Chennai.

Of the total 88 patients who reported to Dr. Rai memorial medical and cancer centre and cancer shelter for treatment of head and neck malignancies, 60 patients, who fulfilled the inclusion criteria, participated in this trial and were Randomly allocated into four groups.

Cobalt 60 is used as the radioactive source that emits gamma rays at an average energy level of 1.2 MeV. In addition, moulds are made for all head and neck malignancy patients undergoing radiotherapy for immobilization of their head during radiation. These patients received external bilateral irradiation, 2 Gys daily, for a total dose of 60 Gys: the doses given five days a week over a period of

6 weeks. The irradiation portals were such that the major salivary glands (parotid and submandibular) were included. Radical resection or de bulking of the primary tumor often preceded the course of irradiation.

Along with radiotherapy, anticancer drugs such as 100mg/m^2 of cisplatin was given on the first day followed by the second dose on the twenty second day and third on the forty third day and 600mg/m^2 of 5-fluorouracil was administered continuously for first five days on weeks one and six respectively. The mouthwashes were numbered randomly from 1 to 60 by the mouth wash manufacture. The mouthwashes assessed were 1) 0:12% chlorhexidine, 2) Salt / sodium bicarbonate, 3) "magic" mouthwash & 4) plain water [control].

Mucositis was assessed using the World Health Organization grading of Mucositis, as it is the most common scale used to assess Mucositis severity. Assessment of Mucositis was done at base line, and after each week of chemoradiation therapy for 6 weeks. Examinations of patients were done under standard illumination and relevant data (name, age, sex, location of cancer, stage of cancer and details regarding the ability to eat solid food) were collected.

The mean ages of patients were estimated and it was found that there existed no statistically significant difference (**p = 0.569)** between the ages of patients in four groups. On evaluating the sex distribution it was found that there existed no statistically significant difference (**p = 0.122)** between the groups based on sex distribution. Location of the cancer were classified as extra oral and intra oral and it was found that there existed no statistically significant difference (**p =**

0.688) between the groups based on the location of cancer. The patients were also grouped based on the staging of cancer, according to TNM classification. Again no statistically significance (**p = 0.895)** was observed between the groups based on the stage of cancer.

Thus, it was found that there existed no statistically significant difference between the patients in four groups, at baseline, based on age, sex, location of cancer and stage of cancer.

Patients were assessed for the mean mucositis scores at weekly intervals and the present study demonstrated that rinsing with "magic" mouthwash reduced the incidence and severity of radiation-induced oral mucositis, when compared to chlorhexidine, salt/soda and placebo mouthwash. The onset of mucositis was also estimated and it was found that the onset of mucositis in control group and the chlorhexidine group is by the end of second week. The salt/sodium bicarbonate group extended till the third week and the "magic" mouthwash group till the fifth week. The onset of mucositis was significantly slow in "magic" mouthwash group when compared to control group and the other test groups **(p = 0.0005)**.

The ability to eat solid food was compared among the four groups. It was found that there was a statistically significant difference (**p = 0.001)** between the control group and the experiment groups in the ability of patients to eat solid food. Chlorhexidine and salt/sodium bicarbonate groups did not have a significant difference between them, and "magic" mouthwash group was found to have a

higher degree of the patient's ability to eat solid food as compared to other experiment groups and the least was seen in the control group.

The conclusions of the present study are:

1. The onset of mucositis was slow in test groups (chlorhexidine, salt/sodium bicarbonate & "magic" mouthwash) as compared to the control group. "Magic" mouthwash was found have delay in onset as compared to other test groups.
2. The ability to eat solid food was high in "magic" mouthwash group compared to all other groups (chlorhexidine, salt/sodium bicarbonate & control groups).
3. The test groups were found to reduce the severity of mucositis compared to control group. "Magic" mouthwash was found to decrease the severity of mucositis compared to other test groups and the control group.

In conclusion, currently, there is no established prophylactic method to decrease chemo radiation – induced oral mucositis. But for preparing the patients by eliminating the foci of infection, proper dental and oral hygiene maintenance and appropriate use of radiation therapy stents and blocks appear to be the best standard approach for these patients followed by a "magic" mouthwash gargling could help the patient to bring down the oral mucositis from 2^{nd} to 6^{th} week with effective healing of the oral mucosa enabling the patient to eat solid food. The study could be conducted in a larger population undergoing chemo radiation which can bring more information to relive the sufferings from chemo radiation induced oral mucositis.

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Just as every action has an equal and opposite reaction, every drug has its own beneficial as well as adverse effects. Radiotherapy like chemotherapy can be compared to a drug which cures cancer, but with its side effects causes debilitating effects on organs. One of the most important and debilitating effects of radiation on normal tissues, which is potentially curable, is radiation induced mucositis. It is seen as an inevitable accompaniment to external beam radiotherapy and mucositis is a painful condition which is debilitating physically and mentally.

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RAGAS DENTAL COLLEGE & HOSPITAL

2/102, EAST COAST ROAD, Uthandi, Chennai – 600119

DEPARTMENT OF ORAL MEDICINE & RADIOLOGY

PROFORMA FOR STUDY TO COMPARE THE EFFICACY & EFFECTIVENESS OF THREE COMMONLY USED MOUTHWASHES TO TREAT CHEMORADIOTHERAPY INDUCED MUCOSITIS

Date:

S.No:

Op.No:

Name: **Age/Sex:**

Address:

Phone number:

Occupation:

Monthly income:

Chief complaint:

History of presenting illness:

Past medical history:

Past surgical history:

Past dental history:

Personal habits:

- **Chewing habits (Duration/ Frequency)**
- **Smoking (Duration / Frequency)**
- **Alcohol consumption (Duration / Frequency)**

General examination:

- **Height / Weight: /**

Local examination:

- **Extra oral (Examination of lymph nodes)**
  - **Number of nodes**
  - **Consistency**
  - **Warmth**
  - **Tenderness**
  - **Mobile / Fixed**

- **Intra oral**

  Gingival

  Labial & buccal mucosa

  Alveolar mucosa

  Tongue

  Palatal mucosa

  Floor of the mouth

  Teeth

Diagnosis:

TNM stage: **Stage I**

Stage II

Stage III

Stage IV

Chemotherapy prescription:

Radiotherapy prescription: **____ Gy in _____ # in _____ weeks**

Radiotherapy delivered with: **Telecobalt / Linac**

Mouthwash: **bottle number -**

Any side effect perceived:

Protocol completed: **yes / no**

Subjective symptoms: **Pain (I / II / III / IV / V / VI weeks)**

Dysphagia (I / II / III / IV / V / VI weeks)

WHO index for grading chemo radiation- induced oral mucositis

	Baseline	1st week	2nd week	3rd week	4th week	5th week	6th week
Buccal Mucosa (R)							
Buccal Mucosa (L)							
Soft Palate							
Hard Palate							
Dorsum of Tongue							
Lateral Border of tongue(R)							
Lateral Border of tongue(L)							
Floor of Mouth							
Score							

CONSENT FORM

I, _____ , the undersigned hereby give my consent for participation as a subject in the study titled "TO COMPARE THE EFFICACY AND EFFECIENCY OF THREE COMMONLY USED MOUTHWASHES TO TREAT CHEMORADIOTHERAPY INDUCED MUCOSITIS" conducted by Dr. P. Jagathesh under the guidance of Capt. Dr. S. Elangovan. Professor, Dept. of Oral Medicine & Radiology, Ragas Dental College & Hospital, Chennai.

I have been counseled about this study and as a part of this study protocol I unconditionally and freely give my consent to participate in this study.

Date:

Place: Signature

ஒப்புதல் படிவம்

நான், ... என்னுடைய முழு ஒத்துழைப்பை மருத்துவர் பா.ஜெகதீஸ் அவர்கள் நடத்தும் "வேதியல் சிகிச்சை மற்றும் ஊடு கதிர்வீச்சால் விளைந்த வாய் புண்ணும் அதனை தீர்க்க உதவும் வாய்க்கருவிகளின் பங்கும்" பற்றிய அறிய உதவும் ஆராய்ச்சிக் கட்டுரைக்கு வழி நடத்தும் மருத்துவர் சு. இளங்கோவன், பேராசிரியர், வாய்மருத்துவம் (ம) கதிர்வீச்சுத்துறை ராகாஸ் பல் மருத்துவக் கல்லூரி (ம) மருத்துவமனை, சென்னை — 119, அவர்களுக்கு அளிக்கின்றேன்.

நான் எனது முழு சுயநினைவோடு, யாருடைய வற்புறுத்தல் இல்லாமலும், யாருடைய கட்டுப்பாட்டின் கீழ் பணியாமலும் என்னுடைய முழு ஒத்துழைப்பையும் இந்த மருத்துவ ஆராய்ச்சிக்காக நல்குகின்றேன்.

இடம் : சென்னை

கையொப்பம

Master Chart

S.No	Age	Sex	Group	Location	Extra/Intra oral	Stage	Onset of mucositis	Ability to eat solid food
1	45	M	CHX	Tongue	Intra oral	III	1st week	No
2	51	M	CHX	Buccal mucosa	Intra oral	III	2nd week	Yes
3	56	M	CHX	Tongue	Intra oral	III	1st week	No
4	69	F	CHX	Tonsil	Extra oral	IV	2nd week	Yes
5	63	M	CHX	Pyriform fossa	Extra oral	IV	1st week	No
6	56	M	CHX	Alveolus	Intra oral	III	2nd week	Yes
7	49	M	CHX	Oropharynx	Extra oral	IV	2nd week	Yes
8	61	M	CHX	Buccal mucosa	Intra oral	IV	1st week	No
9	58	M	CHX	Epiglottis	Extra oral	III	2nd week	Yes
10	52	F	CHX	Nasal cavity	Extra oral	IV	1st week	No
11	57	M	CHX	Tongue	Intra oral	IV	1st week	No
12	49	M	CHX	Maxillary antrum	Extra oral	III	2nd week	Yes
13	61	M	CHX	Alveolus	Intra oral	IV	2nd week	Yes
14	72	F	CHX	Tonsil	Extra oral	IV	2nd week	No
15	55	M	CHX	Pyriform fossa	Extra oral	III	2nd week	No

S.No	Age	Sex	Group	Location	Extra/Intra oral	Stage	Onset of mucositis	Ability to eat solid food
1	48	M	Soda	Tonsil	Extra oral	IV	1st week	No
2	71	M	Soda	Tongue	Intra oral	IV	2nd week	Yes
3	49	F	Soda	Posterior pharyngeal wall	Extra oral	III	2nd week	Yes
4	64	M	Soda	Tongue	Intra oral	III	1st week	No
5	69	M	Soda	Buccal mucosa	Intra oral	IV	3rd week	Yes
6	52	M	Soda	Epiglottis	Extra oral	IV	3rd week	Yes
7	51	F	Soda	Tongue	Intra oral	III	1st week	No
8	39	M	Soda	Pyriform fossa	Extra oral	IV	2nd week	No
9	59	M	Soda	Larynx	Extra oral	IV	1st week	No
10	58	M	Soda	Tongue	Intra oral	III	2nd week	Yes
11	64	M	Soda	Tonsil	Extra oral	IV	1st week	No
12	54	M	Soda	Tongue	Intra oral	IV	3rd week	Yes
13	67	F	Soda	Vocal cords	Extra oral	III	1st week	No
14	48	M	Soda	Tongue	Intra oral	IV	1st week	No
15	61	M	Soda	Buccal mucosa	Intra oral	III	2nd week	Yes

S.No	Age	Sex	Group	Location	Extra/Intra oral	Stage	Onset of mucositis	Ability to eat solid food
1	56	M	“m” M	Buccal mucosa	Intra oral	III	1st week	Yes
2	48	F	“m” M	Oropharynx	Extra oral	IV	3rd week	Yes
3	70	M	“m” M	Epiglottis	Extra oral	III	1st week	No
4	52	M	“m” M	Tongue	Intra oral	IV	2nd week	Yes
5	59	M	“m” M	Hypopharynx	Extra oral	III	5th week	Yes
6	62	M	“m” M	Tongue	Intra oral	III	2nd week	Yes
7	49	M	“m” M	Pyriform fossa	Extra oral	IV	1st week	No
8	58	F	“m” M	Alveolus	Intra oral	III	3rd week	Yes
9	41	M	“m” M	Tonsil	Extra oral	IV	2nd week	No
10	61	M	“m” M	Tonsil	Extra oral	IV	3rd week	Yes
11	69	M	“m” M	Pyriform fossa	Extra oral	III	4th week	Yes
12	71	F	“m” M	Supraglottis	Extra oral	IV	1st week	No
13	53	M	“m” M	Tonsil	Extra oral	III	3rd week	Yes
14	73	M	“m” M	Buccal mucosa	Intra oral	IV	2nd week	Yes
15	43	F	“m” M	Tongue	Intra oral	III	1st week	No

S.No	Age	Sex	Group	Location	Extra/Intra oral	Stage	Onset of mucositis	Ability to eat solid food
1	61	F	Control	Posterior pharyngeal wall	Extra oral	IV	1st week	No
2	54	M	Control	Tongue	Intra oral	III	2nd week	Yes
3	59	M	Control	Buccal mucosa	Intra oral	IV	1st week	No
4	71	M	Control	Pyriform fossa	Extra oral	IV	1st week	No
5	65	M	Control	Tonsil	Extra oral	IV	2nd week	Yes
6	67	F	Control	Tongue	Intra oral	III	1st week	No
7	43	M	Control	Tonsil	Extra oral	IV	1st week	No
8	56	F	Control	Epiglottis	Extra oral	III	1st week	No
9	60	M	Control	Tongue	Intra oral	III	1st week	No
10	58	M	Control	Maxillary antrum	Extra oral	IV	2nd week	Yes
11	49	M	Control	Buccal mucosa	Intra oral	IV	1st week	No
12	58	F	Control	Tongue	Intra oral	III	1st week	No
13	41	F	Control	Buccal mucosa	Intra oral	III	1st week	No
14	55	M	Control	Alveolus	Intra oral	III	1st week	No
15	69	M	Control	Supraglottis	Extra oral	III	1st week	No